State of Oklahoma
Department of Agriculture, Food, and Forestry

J. Kevin Stitt
Governor

Blayne Arthur
Secretary of Agriculture

April 17, 2019

Twanda Maignan, Team Leader
Emergency Response Team
U.S.EPA Office of Pesticide Programs
Document Processing Desk (EMEX)
Room S4900, One Potomac Yard
2777 Crystal Drive
Arlington, VA 22202

Subject: Request for a Section 18 specific exemption for use of **Transform WG Insecticide**, EPA Registration Number 62719-625 to be applied on cotton to control tarnished plant bugs in Oklahoma.

Twanda Maignan:

The Oklahoma Department of Agriculture, Food, and Forestry (ODAFF) requests a specific emergency exemption under the provisions of section 18 of the Federal Insecticide Fungicide and Rodenticide Act, as amended, for the use of Transform WG Insecticide, EPA Registration Number 62719-625 to be applied on cotton to control tarnished plant bugs in Oklahoma.

This is the second year ODAFF has requested a specific emergency exemption for this use using this product.

If you have any questions in connection with this petition, please contact Ryan Williams, (405) 522-5993. Thank you for your consideration of our exemption request.

Respectfully,

Blayne Arthur

Blayne Arthur
Secretary of Agriculture

Enclosures

OKLAHOMA COTTON COUNCIL

Serving the Oklahoma Cotton Industry

809 Willard
Frederick, Oklahoma 73524

March 27, 2019

Mr. Ryan Williams
Oklahoma Department of Agriculture, Food, & Forestry
Certification & Training Administrator
2800 N. Lincoln Blvd.
Oklahoma City, OK 73105

Dear Mr. Williams:

The Oklahoma Cotton Council is writing this letter to request a Section 18 label for Transform WG (sulfoxaflor) insecticide in cotton for the state in 2018. In 2018, planted cotton acreage in Oklahoma doubled from the traditional 250,000 to just over 700,000. Cotton acreage is expected to increase again in Oklahoma in 2019 by perhaps 70,000 acres, bringing the possible 2019 planted acreages to about 900,000. Ultimately, cotton acres treated for insect pests will increase. The Agriculture Division of DowDuPont (just recently renamed Corteva Agriscience) has submitted a request to EPA for a full registration of Transform WG insecticide in cotton for the control of plant bugs, aphids, and stink bugs. We are supportive of this full registration. However, this registration, if approved, is not anticipated to be granted until after the 2019 cotton growing season.

The Oklahoma Cotton Council requests and supports a Section 18 for Transform WG in cotton for the control of plant bugs for the 2019 growing season in Oklahoma. Transform WG provides effective control of this important cotton pest while not being too harsh on beneficial arthropods. Currently there are limited registered products that provide effective control of this pest while not negatively impacting beneficial arthropods and ultimately flaring other pest species. Because of the projected increased cotton acreage across the U.S., effective insecticides my not be in sufficient supply and could leave cotton growers with no product to spray for this pest in 2019. A Section 18 has been granted for cotton in Texas for 2018 and Oklahoma would also like to have this Section 18. This emergency registration is needed by the first of June 2019to have a positive effect on this growing season.

Thank you for your consideration. On behalf of the cotton producers in Oklahoma, we greatly appreciate your assistance with this request.

Sincerely,

Harvey Schroeder
Executive Director

Oklahoma Cooperative Extension Service
Division of Agricultural Sciences and Natural Resources
Oklahoma State University

Department of Entomology and Plant Pathology • 127/110 Noble Research Center
Stillwater, Oklahoma 74078-3033 • (405) 744-5527 • Fax (405) 744-6039
www.ento.okstate.edu

April 9, 2019

Ryan Williams
Oklahoma Department of Agriculture, Food, & Forestry Certification
& Training Administrator 2800 N. Lincoln Blvd.
Oklahoma City, OK 73105

Ryan:

I am writing this letter in full support of a request for a Section 18 registration for sulfoxaflor for use from May through October to control cotton fleahopper, *Pseudatomoscelis seriatus,* which is a serious and established pest of all cotton-growing counties in Oklahoma. In Oklahoma, typical planting dates are from 11 May through 10 June, and harvest dates are from 15 October through 01 December for cotton.

In 2017, producers harvested ca. 1.06 million bales of cotton on 550,000 acres in Oklahoma, worth about $362.3 million. In 2018, cotton was planted on 780,000 acres, and intentions for 2019 are that ca. 790,000 acres will be planted in 2019. As cotton acreage increases, the pressure from pests such as cotton fleahopper and other plant-sucking bugs will increase. Pest surveys conducted in Oklahoma in 2017 suggest that cotton fleahopper infested more than 416,000 acres and that more than 360,000 acres were treated for their control. Despite that, estimated crop losses from cotton fleahopper exceeded $10 million. In addition, infestations of tarnished plant bug, *Lygus lineolaris* are possible, due to the anticipated increase in cotton planting. While not considered as important a pest as the cotton fleahopper, it also has the potential for significant yield loss, and is a common insect pest of alfalfa in Oklahoma, where many of the new acres will be planted.

Transform provides effective (80% or more) control of cotton fleahopper and tarnished plant bug up to 20 days post application. In addition, it is highly effective (98% on cotton aphids after 7 days and 90% after 15 days). Most currently registered products used for cotton fleahopper control are either pyrethroids (IRAC class 3) or organophosphates (IRAC class 1B). While registered pyrethroid insecticides are often used to control cotton pests, their activity is very broad-spectrum and are very hard on resident natural enemies. They have become increasingly ineffective, and because of their impact on natural enemies, have the potential to cause secondary outbreaks of spidermites and aphids. History has shown that reliance on one class of active ingredients for control sets up a high potential for selection of insecticide-resistant aphids and bollworm/budworms, and is NOT a component of sound integrated pest management (IPM). I fully support this request.

Sincerely,

Tom A. Royer

Tom A. Royer
Extension Entomologist and IPM Coordinator

Dow AgroSciences

Dow AgroSciences LLC
9330 Zionsvile Road
Indianapolis, IN 46163

dowagro.com

April 8, 2019

Ryan Williams
Oklahoma Department Of Ag., Food, & Forestry
Certification & Training Administrator
2800 N. Lincoln Blvd.
Oklahoma City, Ok 73105

Re: Support letter for Transform™ WG Section 18 on cotton

Dear Mr. Williams,

Per your request, this letter is to confirm that Dow AgroSciences supports the pursuit of a Section 18 emergency exemption for Transform WG to control plant bugs in cotton in the state of Oklahoma. Transform WG has provided excellent efficacy against plant bugs in previous use under Section 18 exemptions, with no negative impacts on non-target insects. It also represents a new class of chemistry with a novel mode of action, and controls pests resistant to other classes of chemistry.

If you have questions, please do not hesitate to call me.

Sincerely,

Jamey Thomas, Ph.D.
US Regulatory Manager
Dow AgroSciences

cc: Tami Jones-Jefferson, DAS

2018 FIFRA SECTION 18

General information requirements of §40 CFR 166.20(a) in an application for a specific exemption.

TYPE OF EXEMPTION BEING REQUESTED

✓ SPECIFIC

QUARANTINE

PUBLIC HEALTH

SECTION 166.20(a)(1): IDENTITY OF CONTACT PERSONS

i. This application to the Administrator of the Environmental Protection Agency (EPA) for a specific exemption to authorize the use of Sulfoxaflor (Transform® WG Insecticide, EPA Reg. No. 62719-625) to control the Tarnished Plant Bug, *Lygus lineolaris*, in cotton by the Oklahoma Department of Agriculture, Food, & Forestry. Any questions related to this request should be addressed to:

Ryan Williams
Oklahoma Department of Agriculture, Food, & Forestry
Pesticide Program Administrator
2800 N. Lincoln Blvd.
Oklahoma City, Ok
Phone: (405) 522-5993
Fax: (405) 522-5986
Email: ryan.williams@ag.ok.gov

ii. The following qualified experts are also available to answer questions:

University Representatives:
Tom Royer, PhD
IPM Coordinator
Oklahoma State University
127 NRC
Stillwater, Ok 74078
405-744-9406
tom.royer@okstate.edu

Registrant Representative:
Tami Jones-Jefferson
U.S. Regulatory Leader
U.S. Regulatory & Government Affairs - Crop Protection
Dow AgroSciences
9330 Zionsville Road
Indianapolis IN 46268
phone: 317.337.3574
email: tjjonesjefferson@dow.com

SECTION 166.20(a)(2): DESCRIPTION OF THE PESTICIDE REQUESTED

i. **Common Chemical Name (Active Ingredient):** Sulfoxaflor

Trade Name and EPA Reg. No.: Transform® WG Insecticide, EPA Reg. No. 62719-625

Formulation: Active Ingredient 50%

SECTION 166.20(a)(3): DESCRIPTION OF THE PROPOSED USE

i. Sites to be treated:
The insecticide will be restricted to use on cotton fields in the state of Oklahoma for the purpose of controlling the tarnished plant bug, Lygus lineolaris (Palisot de Beauvois) statewide.

ii. Method of Application:
Applications will be made by foliar application.

iii. Rate of Application:
1.5 – 2.25 oz/ac (0.047 – 0.0071 lb ai/ac). Annual use will not exceed 8.5 oz. of Transform (0.266 lb. ai/ac).

iv. Maximum Number of Applications:
4 application per acre per year and the total amount of Transform WG not exceeding 8.5 fl oz (0.266 lb a.i. of sulfoxaflor) per acre per year.

v. Total Acreage to be Treated:

There is projected to be 500,000 – 800,000 acres of cotton planted.

vi. Total Amount of Pesticide to be used:

Maximum amount of product to be applied:

$$\frac{800{,}000\text{acres} \times 4\ \text{applications/crop} \times 8.5\ \text{fl oz/acre/application}}{128\ \text{fl oz / gallon}} = 212{,}500\ \text{gallons}$$

vii. Restrictions and Requirements:

- **Preharvest Interval:** Do not apply within 14 days of harvest.
- Minimum Treatment Interval: Do not make applications less than 5 days apart.
- Do not make more than four applications per acre per year.
- Do not apply more than a total of 8.5 fl. oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.

Duration of the Proposed use:
May 1st through October 30th, 2019

viii. Earliest Possible Harvest Date:
September 30th, 2019

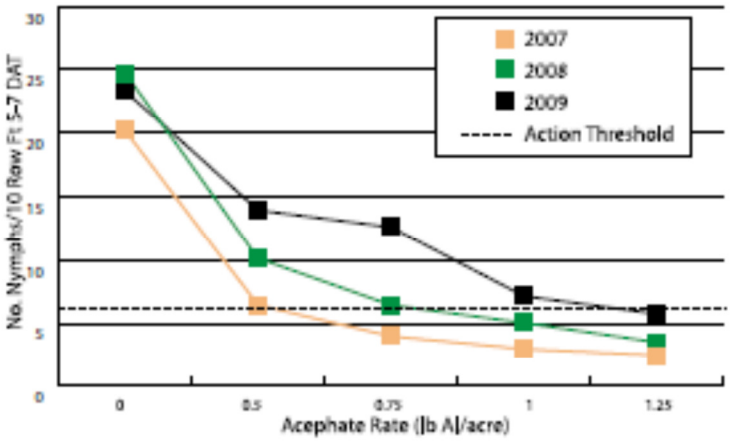
SECTION 166.20(a)(4): ALTERNATIVE METHODS OF CONTROL

Registered Alternative Pesticides:

Baythroid, Carbine, Centric, Malathion, Mustang MAXX, Steward, Triple Crown, Vydate

Chemical control strategies remain the primary tool used to manage this pest. Presently, numerous insecticides are recommended against tarnished plant bug, but varying levels of resistance has been documented to nearly every class of these compounds among Mid-South (Arkansas, Louisiana, Mississippi, Tennessee) populations of this insect. Populations have demonstrated resistance to pyrethroids and some organophosphates for several years (Snodgrass and Gore 2007), but many populations remained susceptible to neonicotinoid insecticides including thiamethoxam and imidacloprid (Snodgrass et al. 2008). Acephate has been the most widely used and effective insecticide for control of plant bugs in cotton but efficacy continues to decrease in Louisiana and much of the mid South. Three years of study by Copes et al. (2010) clearly shows that acephate efficacy is rapidly eroding across Louisiana (Figure 1, Copes et al. 2010).

Fig. 1. Three years, 2007-2009 of acephate efficacy
Against the TPB in Louisiana field trials. The dotted
Line indicates the action threshold of 6/ 10 row ft.



Even though acephate expressed partial efficacy against tarnished plant bugs in Arkansas, higher rates (0.5 to 1.25 lb AI/acre) were necessary each year from 2007-2009 to maintain the infestations below the action threshold. The highest rate actually exceeded the labeled rate that could be used. These field efficacy results are supported by laboratory data from Snodgrass which show significant levels of OP resistance in tarnished plant bug populations throughout the hills and delta in Arkansas, Louisiana, and Mississippi. During the past two years, populations in these states also have been expressing lower susceptibility to neonicotinoid products, but no high levels of resistance have been documented. (Snodgrass 2010 abstract, See Appendix A).

In our regional plant bug trial conducted in 2009-2010 the following list of currently labeled products were used to evaluate their efficacy against tarnished plant bug in the Midsouth (Table 1):

Table 1. Regional treatment list of currently labeled products tested.

Product	Formulation	Rate/ Acre
1. UTC		
2. Acephate	90 S or 97	0.75 lb
3. Bidrin	8 EC	6 oz
4. Vydate	3.77 C-LV	12 oz
5. Centric	40 WG	2 oz
6. Trimax Pro	4.44 SC	1.5 oz
7. Carbine	50 WG	2.5 oz
8. Leverage	2.7 SE	4.5 oz
9. Intruder	70 WP	1.1 oz
10. Endigo	2.06 ZC	5.0 oz
11. Diamond	0.83 EC	9.0 oz
12. Brigade	2 EC	5.12 oz

Cook et al. (2007) showed that standard insecticide use strategies can reduce tarnished plant bug numbers, but none are consistently effective and can maintain sub-economic injury levels for the season. During 2009 and 2010, the regional (Arkansas, Louisiana, Mississippi, and Tennessee) full-season insecticide screen was used to evaluate a list of products for control of tarnished plant bug (Fig 2, Lorenz et al., 2009 unpublished). As the data indicates no treatment of currently

labeled products were able to lower plant bug numbers below the threshold of 6 plant bugs per 10 row feet at 6-10 days following the second application. (Figure 3, Lorenz et al. 2010 unpublished).

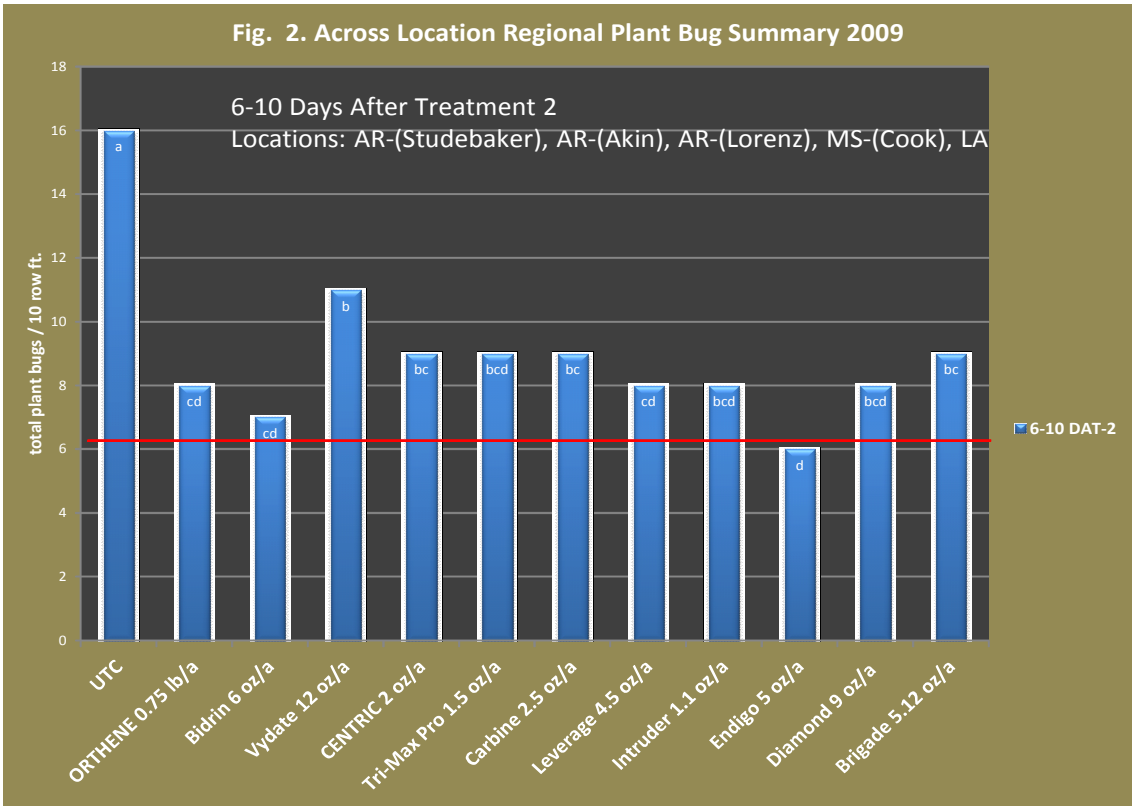


Figure 2. Regional plant bug efficacy trial summary across states, 2009.

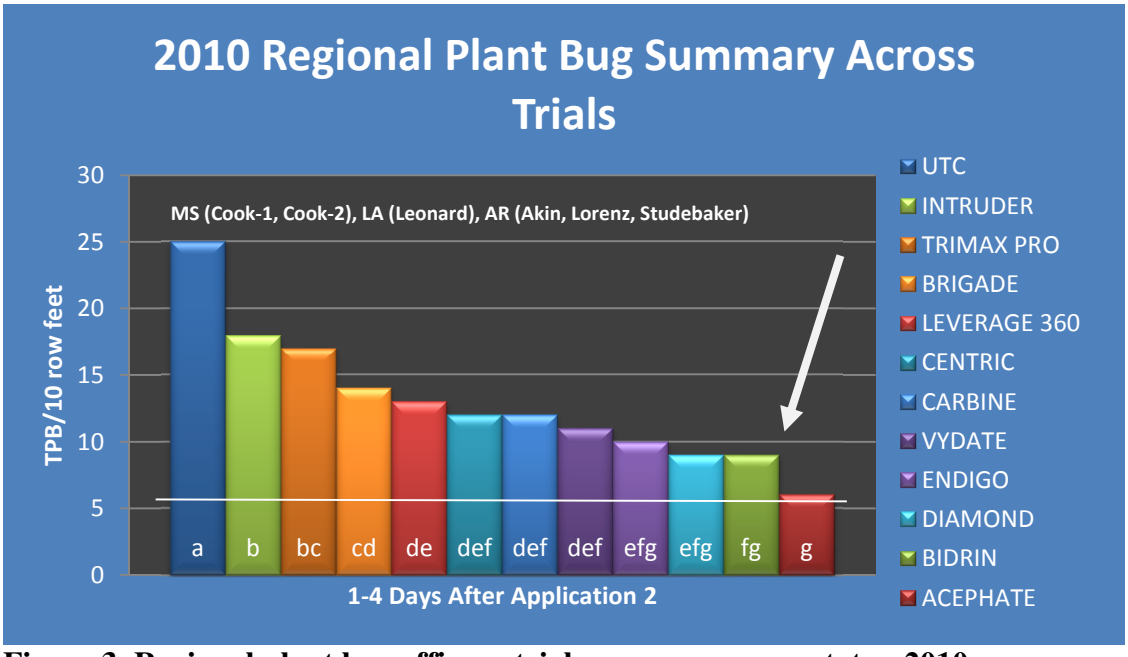


Figure 3. Regional plant bug efficacy trial summary across states, 2010.

In 2010 the figure above shows the lack of control for all currently labeled products for control of plant bugs in MS, LA and 3 locations in AR (Fig. 3).

Six sprays were applied to the Louisiana trial which was designed to simulate moderate to high pest infestation levels, typical of the situation in many Louisiana and Mid-South cotton fields (Figure 4, Sharp et al. 2010 and B. R. Leonard unpublished).

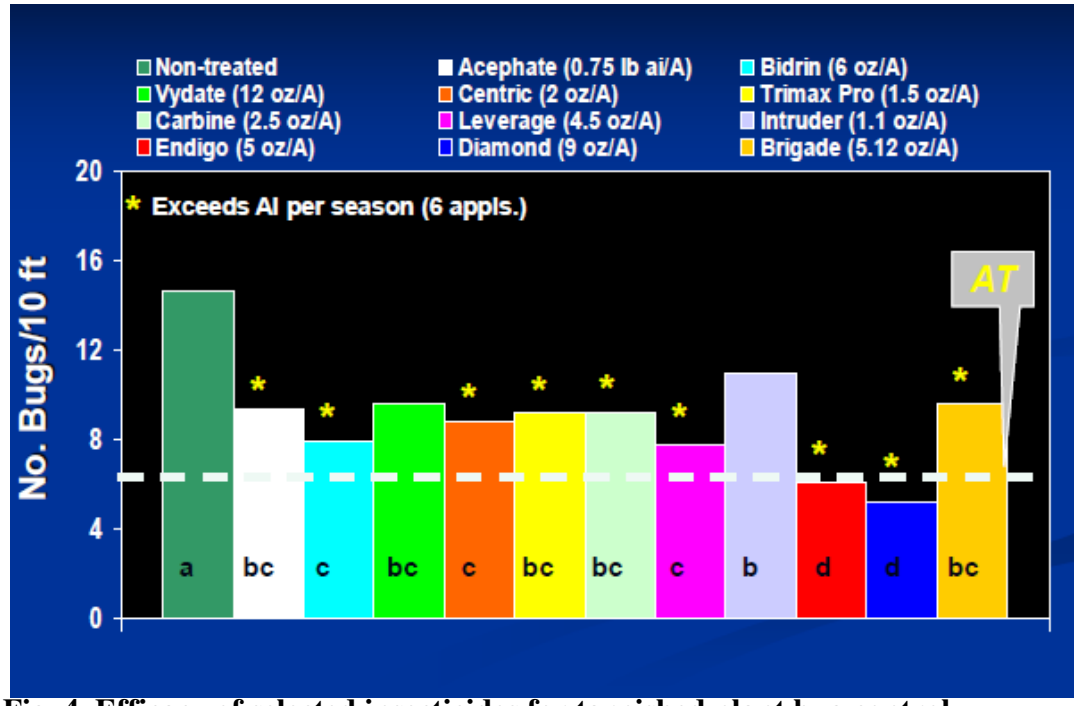


Fig. 4. Efficacy of selected insecticides for tarnished plant bug control.

Using seasonal means of tarnished plant bug nymphs as a metric for insecticide efficacy, all treatments significantly reduced numbers relative to a non-treated control. However, only Endigo and Diamond successfully reduced numbers below the action threshold (line marked with AT) used to gauge the need for additional treatments to stop yield losses. In addition, all of the bars highlighted with an asterisk (*) illustrate that six applications of those treatments exceeded the total allowable seasonal AI/acre. Only Vydate and Intruder AI's were not exceeded. Yield losses have become severe in these situations in spite of multiple insecticide sprays. Currently, the only chemical strategy recommended is to co-apply two insecticides and rotate among chemical classes.

In some areas across Arkansas and the Mid-South region, tarnished plant bug infestations have reached outbreak levels and become uncontrollable. In Mississippi during 2007, producers averaged approximately 7-10 insecticide applications for this pest (Catchot 2007). The highest insecticide application frequency in Mississippi prior to 2007 was 5.2 sprays per year and occurred during 2004 in that state. Arkansas producers averaged 3.5 applications during 2007 (Williams 2008) for this pest, but some areas received 8-10 treatments. In 2011 the average number of applications for this pest increased to 5 applications with some areas reporting 8 or more applications. Current trends with insecticide resistance and lack of effective alternative

technologies will allow problems with tarnished plant bug management to intensify across Arkansas and the Mid-South states. Chemical control options that provide consistent efficacy are not available to manage this pest. Effective Lygus control is a serious, unmet need for Mid-South cotton growers and one that requires immediate and urgent action. This has now become an emergency situation.

These results have shown that regardless of the registered insecticide, tarnished plant bug populations in these states have become significantly more difficult to control using common recommended insecticides (Lorenz et al. 2009; Moore et al. 2010). As a result, the numbers of applications and use rates needed to control tarnished plant bug have increased. With a novel mode of action and chemical class, sulfoxaflor will successfully control both insecticide-susceptible and -resistant populations of tarnished plant bug, thereby improving the overall cotton IPM system. This would be a tremendous economic opportunity for cotton growers, and more environmentally-friendly alternative to the sustained frequency of the currently used products.

As expected, the excessive use of some products for tarnished plant bug are now beginning to induce additional pest problems (spider mites and cotton aphids) in some areas. This is of great concern to many producers and pest management practitioners. Organophosphate, carbamate and pyrethroid insecticides can impact natural beneficial arthropod populations and flare secondary insects. Acephate is commonly used for Lygus control and can flare aphids and mites. Pyrethroid insecticides may flare aphids and mites, as well. Sulfoxaflor should reduce the frequency of selected insecticides used, especially acephate, dicrotophos, and oxamyl. The ecological and toxicological profile of sulfoxaflor is considered to be more favorable than the ecological and toxicological profiles of these insecticides. Limited data currently suggest that sulfoxaflor is not likely to flare aphids and mites. A comparison of the years 2008-2011 and 2012-2015 indicate that Arkansas has seen a yield increase of 15% while acreage has decreased by 38%, however, the number of tarnished plant bug applications has increased by 33% ~1.6 more applications per season (Table 2.):

Table 2. Comparison of 2008-2011 prior to Transform and 2012-2015 with Transform in Arkansas.

Pre Transform Use In Arkansas				**Post Transform Use in Arkansas**			
Year	**Yield**	**Acres**	**TPB Sprays**	**Year**	**Yield**	**Acres**	**TPB Sprays**
2008	1012	615000	1.9	2012	1064	585000	5.1
2009	818	500000	2.9	2013	1133	305000	6
2010	1045	540000	2.8	2014	1145	330000	6
2011	929	660000	4.4	2015	1112	205000	6
Percent Change Pre and Post Transform Use					**15%**	**-38%**	**33%**

ii. A detailed explanation of why alternative practices, if available, either would not provide adequate control or would not be economically or environmentally feasible.

Several IPM strategies are recommended for controlling tarnished plant bug in cotton (Gore et al. 2008). Non-chemical tactics include area-wide control of non-crop alternate hosts and selected host plant resistance traits. Proper selection of varieties and managing the optimum planting

period are being to produce a rapid fruiting and early maturing crop; thereby reducing the time the crop is susceptible to this pest. Careful insecticide application timing based upon revised spray action thresholds are used to precisely target populations before they reach outbreak levels. All of these practices are currently in place and are being used by cotton producers. However, these strategies only serve to suppress populations and are not effective as stand-alone practices. Effective chemical control practices are still necessary to provide tarnished plant bug management in cotton.

Over the last ten years, field use rates have more than doubled and control has continued to decline. This has put a tremendous amount of pressure on the neonicotinoid class. Of that class, thiamethoxam is by far the most effective for tarnished plant bug control. Consequently, two to four pre-flower applications in cotton target both tarnished plant bugs and cotton aphids. Centric (thiamethoxam) has been the insecticide of choice in this situation because it provides better control of the whole pest complex than other neonicotinoids at that time of the year. The most common rate used at that time of year is 2 oz formulated product per acre (0.05 lbs ai/A). The maximum seasonal use rate for Centric is 5.0 oz (0.125 lb ai thiamethoxam). Therefore, two applications of Centric at 2 oz/A (0.05 lbs ai per acre per application) during the pre-flowering period does not leave enough active ingredient for later applications of either Centric or Endigo (thiamethoxam + lambda-cyhalothrin). Recently the control observed with Centric has declined and is not as effective in recent years. USDA has reported increased tolerance to thiamethoxam (pers comm 2016). The only other labeled insecticides available are Carbine (flonicamid) and Diamond (novaluron). Figure 4 above shows typical results observed with Carbine in Mississippi and other mid-South states for tarnished plant bug. Diamond is the only other insecticide available for late season tarnished plant bug control. As mentioned previously, Diamond is an insect growth regulator that only controls the immature stages. Therefore, Diamond applications are exclusively used with another class of chemistry to control adults. Also, application timing is critical with this insecticide and applications are often sprayed too late to provide the most effective levels of control. Therefore, the use of one or two applications of Transform will provide significant economic benefits for cotton growers in Arkansas.

SECTION 166.20(a)(5): EFFICACY OF USE PROPOSED UNDER SECTION 18

This product provides 80-98% Control. Yields in Oklahoma are not available, but in neighboring states, Transform can preserve 20-40% of yield potential compared to other insecticides.

Value of Transform in an Overall IPM Approach for Tarnished Plant Bug in Cotton:
Sulfoxaflor (DAS test code GF-2372, proposed trade name Transform^{TM}) has been evaluated in laboratory and field trials for the past several years. Recent publications by Babcock et al. (2010, See Appendix B) and Zhu et al. (2010, See Appendix C) clearly define the biology and biochemistry of sulfoxaflor and demonstrate a novel mode of action against sap feeding insects including those in the order Heteroptera. Insects in the genus *Lygus* are included this order. Sulfoxaflor-induced mortality was similar between insecticide-resistant and –susceptible strains of several Homoptera and Heteroptera. No cross-resistance was detected to sulfoxaflor in

populations expressing resistance to a broad range of modes of action. The effectiveness of sulfoxaflor against insecticide-susceptible populations of tarnished plant bug, *Lygus lineolaris* (Palisot de Beauvois) was comparable to those of other labeled classes of insecticides. These research projects support a novel mode of action for sulfoxaflor including those insecticides with similar chemical structures (neonicotinoids).

Numerous field trials were performed during 2008-2010 across the Mid-South States and in Arkansas (Appendix D) against tarnished plant bug and are in the process of being published, trial results showed that Sulfoxaflor was usually as good as standards but often much better. The first field results were reported by Smith et al. (2010, See Appendix E) for Mississippi trials and show levels of efficacy comparable to or significantly better than standards (acephate, Bifenthrin, thiamethoxam) on one or more sample periods against tarnished plant bug nymphs. For Louisiana during 2009-2010, Hardke (2011, Submitted to Entomological Society of America's Arthropod Management Tests, See Appendix F) summarized the results of field trials for sulfoxaflor performance against tarnished plant bug. In the 2009 trials, effective rates and application frequencies were defined compared to standard products. In a co-application trial with a pyrethroid-resistant population, sulfoxaflor outperformed Endigo and Bifenthrin (alone) on one or more post-treatment evaluation dates. Based upon total insects during 2010, sulfoxaflor at the upper rate and in combination with novaluron demonstrated significantly better control of tarnished plant bugs than acephate and efficacy equivalent to a combination of a pyrethroid and thiamethoxam (Endigo). Reports of additional field trials from Arkansas, Mississippi, and Tennessee are in preparation and will serve to support the Louisiana results.
A multi-state (AR, LA, MS, TN) summary of field trials against "high pressure" tarnished plant bug infestations on cotton during 2008-2010 is reported in Appendix G. These results demonstrated sulfoxaflor at one or more rates demonstrated control of plant bugs (high population levels) superior to the OP, dicrotophos. The residual efficacy of sulfoxaflor was greater than that for both dicrotophos and thiamethoxam. Efficacy was similar to a co-application of a pyrethroid + neonicotinoid. In a comparison of cotton yields among treatments for these trials, sulfoxaflor was similar to that of acephate (Acephate is broader spectrum and may have provided some yield increase from additional caterpillar pest control). Pest management practitioners recognize that sulfoxaflor should not be used as a single, season-long treatment, so chemical control strategies with co-applications and/or rotation for sequential treatments are the logical use pattern.
Other studies conducted in Arkansas show the yield loss associated with the current standard (acephate) and the increased yield of sulfoxaflor, well exceeding 20% in 2009 (Table 3.) and up to 46% in 2010 (Table 4).

Table 3. Efficacy and yield comparison of selected Transform rates and acephate, 2009.

Transform Trial 2009			
Treatments	Season Total Plant Bugs	Harvest Lint lbs/acre	% Yield above UTC
Transform 0.045 lb ai/a AB	59.3 d	587 a	126%
Transform 0.022 lb ai/a AB	108 c	538 ab	107%
Transform 0.034 lb ai/a AB	79 d	522 ab	101%
Orthene 1 lb/a A	178.3 b	475 bc	83%
UTC	276.3 a	260 d	

Table 4. Efficacy and yield comparison of selected Transform rates and acephate, 2010.

PB5-2010				
Treatment	**Plant Bugs 3DAT**	**Season Total Plant Bugs**	**Yield lint lbs/acre**	**% Yield above UTC**
Transform 0.045 lb ai/a	18.3 cd	93.3 c	1231 a	36%
Endigo 5 oz/a	18.8 cd	105.5 c	1136 ab	26%
Bidrin 6 oz/a	6.3 d	100.5 c	1100 ab	22%
Transform 0.067 lb ai/a	17.5 cd	86.5 c	1065 abc	18%
Acephate 0.5 lb./acre	53.8 b	185 b	833 c	-8%
Untreated Check (UTC)	105.8 a	309.8 a	903 bc	

When sulfoxaflor was evaluated as a component of this type of strategy, those use patterns with sulfoxaflor maintained tarnished plant bug populations below the action threshold for the duration of the trial; whereas a standard strategy was unable to provide satisfactory control. In a commercial field, the standard treatments (without sulfoxaflor) would have required additional applications to reduce populations. In the season-long trials, strategies relying on sulfoxaflor significantly increased cotton yield above the standard-treated and non-treated plots. Willrich et al. (2010, see Appendix H) further summarized results for 2008-2009 as an abstract and reported sulfoxaflor's acute toxicity for knockdown of tarnished plant bug infestations at ≤ 5 d and residual control extending for ≥ 7 d. In addition, cotton treated with sulfoxaflor produced lint yields equal to or superior than cotton treated with acephate (1.0 lb AI/acre) across 16 trials. Recent trial results continue to show the efficacy of Transform has not diminished as shown in the Tables 5 and 6 below from a trial conducted in 2014 and 2015, respectively.

Table 5. Efficacy of selected insecticides for control of tarnished plant bug showing total plant bugs sampled, yield and yield reduction compared to Transform. 2014.

Treatment	Season Total Plant Bugs	Yield lbs/acre	% below
Transform 1.75 oz	19	5326.6	
UTC	149	2499	-53
Bidrin 6 oz/acre*	38	4237.9	-20
Brigade 5.6 oz/acre*	70.4	3598	-32
Sivanto 14 oz/acre	85	2804.8	-47
Vydate C-LV 10.7 oz/acre	51	3151.8	-41
DoubleTake 4 oz/acre	143	2473.8	-54

Table 6. Efficacy of selected insecticides showing total number of plant bugs sampled, yield and percentage of reduced yield compared to Transform. 2015.

Treatment	Season Total Plant Bugs	Yield pounds/acre	% below
Transform 1.75 oz	45	4157	
UTC	140	3244.1	-22%
Strafer 3 oz	61	3307.2	-20%
Centric 2 oz	75	3387.4	-19%
Centric 2 oz & Diamond 6 oz	65	3426.1	-18%
Orthene 1 lb	46	3335.8	-20%

Transform averaged about 20% better control and the same for increased yield over other treatments.

Value of Transform in an Overall IPM Approach for Tarnished Plant Bug in Cotton

Multiple experiments have been conducted throughout Mississippi to evaluate an overall integrated pest management approach for tarnished plant bug in cotton and the importance of various insecticides in that approach. Inconsistent control with most of the currently labeled insecticides due to documented resistance highlighted above has forced growers to adopt multiple best management practices to economically manage tarnished plant bug. Although these best management practices have improved tarnished plant bug management, insecticides remain an important component. In particular, the registration of sulfoxaflor in 2012 (Section 18 in 2012 and Section 3 in 2013-15) increased the adoption of the overall IPM approach.

Sulfoxaflor rapidly became the foundation for the IPM approach because of its high level of efficacy against tarnished plant bug and the relative safety for beneficial insects (Fig. 5). Even at very high use rates (100 g ai/ha=3.0 oz./A), significantly more beneficial arthropods were conserved compared to the pyrethroid (Warrior) and the organophosphate (Orthene). Similar results were observed by Kerns et al. (2011) where densities of convergent lady beetles for

sulfoxaflor were not significantly different than Carbine. Both the Carbine and sulfoxaflor had significantly lower densities than the untreated control which was most likely due to the reduction in prey (cotton aphid) in the treated plots.

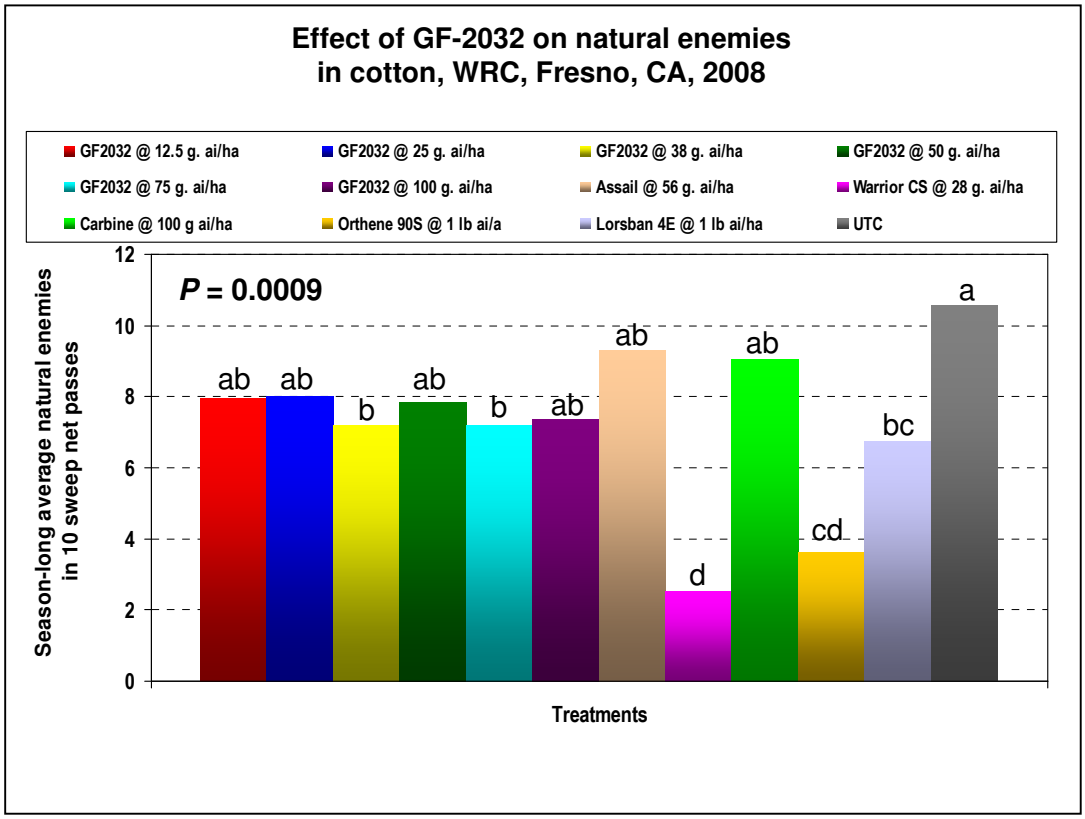


Figure 5. Impact of various rates of sulfoxaflor and other insecticides on natural enemy populations in cotton in California.

Although natural enemy populations provide little benefit for tarnished plant bug management, sprays with high rates of organophosphates and pyrethroids (usually applied as a tank mix) targeting tarnished plant bug reduce natural enemy populations and "flare" other pests such as two spotted spider mite or cotton aphid. A study conducted in Stoneville, MS in 2013 compared overall management programs. The treatments included cotton grown with all classes except neonicotinoids or sulfoxaflor, all classes except sulfoxaflor, and all available classes. Overall, one to two applications were needed for two spotted spider mite in the treatments where sulfoxaflor was not used (Figure 6). Additionally, the treatments that did not include sulfoxaflor each needed to be sprayed separately for cotton aphid (Figure 6). A portion of this is due to sulfoxaflor control of cotton aphids, but preservation of beneficial insects also contributed. In summary, the use of sulfoxaflor for tarnished plant bug management can reduce the number of insecticide applications targeting other pests because of the lower toxicity to beneficial arthropods. Overall, yields and economic returns were greater where all classes of insecticides were included.

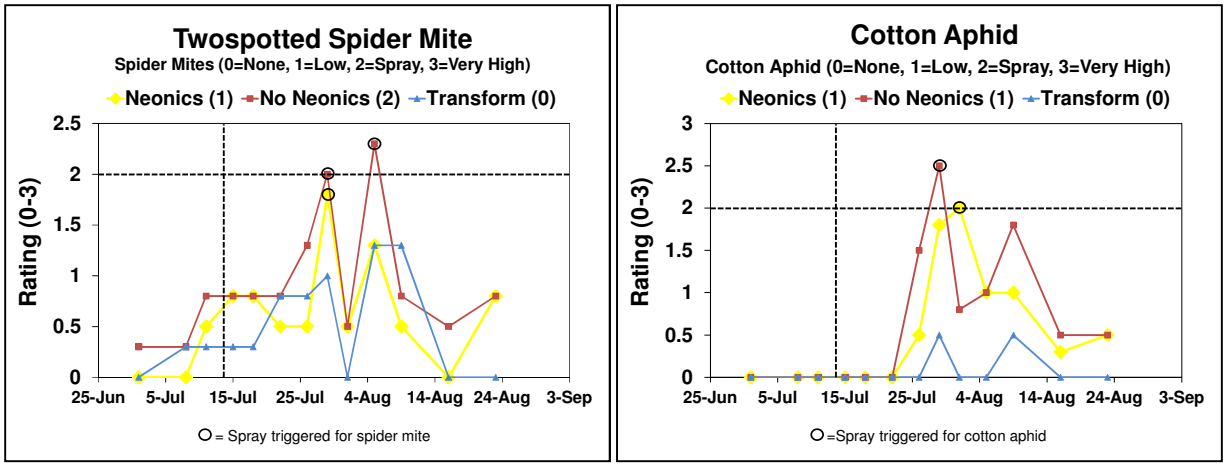


Figure 6. Impact of insecticide use programs for tarnished plant bug management on the number of insecticide sprays for two spotted spider mite and cotton aphid.

The tarnished plant bug IPM program has been important for increasing the profitability of cotton programs in Mid-South cotton. However, diversity in the available classes of insecticides available to manage tarnished plant bug is critical to make the overall IPM approach successful. In particular, insecticides that provide high levels of efficacy against tarnished plant bug that do not flare other pests provide the foundation for the overall cotton IPM program. Two insecticides have proven to be very important in this respect. Research throughout the Mid-South has shown that a single application of the insect growth regulator, novaluron, can provide long term benefits for tarnished plant bug management. However, novaluron does not control adult plant bugs and it consistently flares cotton aphids. As a result, sulfoxaflor is the ideal insecticide to use as one to two applications immediately following the novaluron application. Additionally, the registration of sulfoxaflor provided growers with a legitimate insecticide rotation strategy to make the tarnished plant bug IPM program successful.

All available data indicates that sulfoxaflor is an alternative product to the insecticides currently used to manage tarnished plant bug on cotton. It is an excellent tool for Arkansas and Mid-South cotton IPM programs by improving efficacy, reducing input costs, and increasing yields. This compound has a selective spectrum of activity, has not flared other pests, can be used as a rotational partner with other chemistries, and has demonstrated value against insecticide-resistant populations. Sulfoxaflor is the backbone of chemical control strategies for tarnished plant bug and is desperately needed in this emergency situation. Sulfoxaflor has been widely adopted by producers because of safety to pollinators and other beneficial insects. Two of the largest beekeepers in Arkansas have shown their support for Transform use on cotton (Attachment 2 & 3). This product has allowed growers to further implement IPM programs due to the safety profile. Additionally, since its use in 2012 in cotton there has not been a single incident reported with managed bees. It also provides for insecticide resistance management which is, or should be, a concern for everyone.

SECTION 166.20(a)(6): EXPECTED RESIDUES FOR FOOD USES

Michael Hare, Ph.D.

Acute Assessment

Food consumption information from the USDA 1994-1996 and 1998 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII) and maximum residues from field trials rather than tolerance-level residue estimates were used. It was assumed that 100% of crops covered by the registration request are treated and maximum residue levels from field trials were used.

Drinking water. Two scenarios were modeled, use of sulfoxaflor on non-aquatic row and orchard crops and use of sulfoxaflor on watercress. For the non-aquatic crop scenario, based on the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) and Screening Concentration in Ground Water (SCI-GROW) models, the estimated drinking water concentrations (EDWCs) of sulfoxaflor for acute exposures are 26.4 ppb for surface water and 69.2 ppb for ground water. For chronic exposures, EDWCs are 13.5 ppb for surface water and 69.2 ppb for ground water. For chronic exposures for cancer assessments, EDWCs are 9.3 ppb for surface water and 69.2 ppb for ground water. For the watercress scenario, the EDWCs for surface water are 91.3 ppb after one application, 182.5 ppb after two applications and 273.8 ppb after three applications.

Dietary risk estimates using both sets of EDWCs are below levels of concern. The non-aquatic-crop EDWCs are more representative of the expected exposure profile for the majority of the population. Also, water concentration values are adjusted to take into account the source of the water; the relative amounts of parent sulfoxaflor, X11719474, and X11519540; and the relative liver toxicity of the metabolites as compared to the parent compound.

For acute dietary risk assessment of the general population, the groundwater EDWC is greater than the surface water EDWC and was used in the assessment. The residue profile in groundwater is 60.9 ppb X11719474 and 8.3 ppb X11519540 (totaling 69.2 ppb). Parent sulfoxaflor does not occur in groundwater. The regulatory toxicological endpoint is based on neurotoxicity.

For acute dietary risk assessment of females 13-49, the regulatory endpoint is attributable only to the parent compound; therefore, the surface water EDWC of 9.4 ppb was used for this assessment.

A tolerance of 0.3 ppm for sulfoxaflor on grain sorghum has been established. There is no expectation of residues of sulfoxaflor and its metabolites in animal commodities as a result of the proposed use on sorghum. Thus, animal feeding studies are not needed, and tolerances need not be established for meat, milk, poultry, and eggs.

Drinking water exposures are the driver in the dietary assessment accounting for 100% of the exposures. Exposures through food (sorghum grain and syrup) are zero.

The acute dietary exposure from food and water to sulfoxaflor is 16% of the aPAD for children 1-2 years old and females 13-49 years old, the population groups receiving the greatest exposure.

Chronic Assessment

The same refinements as those used for the acute exposure assessment were used, with two exceptions: (1) average residue levels from crop field trials were used rather than maximum values and (2) average residues from feeding studies, rather than maximum values, were used to derive residue estimates for livestock commodities. It was assumed that 100% of crops are treated and average residue levels from field trials were used.

For chronic dietary risk assessment, the toxicological endpoint is liver effects, for which it is possible to account for the relative toxicities of X11719474 and X11519540 as compared to sulfoxaflor. The groundwater EDWC is greater than the surface water EDWC. The residue profile in groundwater is 60.9 ppb X11719474 and 8.3 ppb X11519540. Adjusting for the relative toxicity results in 18.3 ppb equivalents of X11719474 and 83 ppb X11519540 (totaling 101.3 ppb). The adjusted groundwater EDWC is greater than the surface water EDWC (9.3 ppb) and was used to assess the chronic dietary exposure scenario.

The maximum dietary residue intake via consumption of sorghum commodities would be only a small portion of the RfD (<0.001%) and therefore, should not cause any additional risk to humans via chronic dietary exposure. Consumption of sorghum by sensitive sub-populations such as children and non-nursing infants is essentially zero. Thus, the risk of these subpopulations to chronic dietary exposure to sulfoxaflor used on grain sorghum would be insignificant.

The major contributor to the risk was water (100%). There was no contribution from grain sorghum to the dietary exposure. All other populations under the chronic assessment show risk estimates that are below levels of concern.

Chronic exposure to sulfoxaflor from food and water is 18% of the cPAD for infants, the population group receiving the greatest exposure. There are no residential uses for sulfoxaflor.

Short-term risk. Because there is no short-term residential exposure and chronic dietary exposure has already been assessed, no further assessment of short-term risk is necessary, the chronic dietary risk assessment for evaluating short-term risk for sulfoxaflor is sufficient.

Intermediate-term risk. Intermediate-term risk is assessed based on intermediate-term residential exposure plus chronic dietary exposure. Because there is no residential exposure and chronic dietary exposure has already been assessed, no further assessment of intermediate-term risk is necessary.

Cumulative effects. Sulfoxaflor does not share a common mechanism of toxicity with any other substances, and does not produce a toxic metabolite produced by other substances. Thus, sulfoxaflor does not have a common mechanism of toxicity with other substances.

Cancer. A nonlinear RfD approach is appropriate for assessing cancer risk to sulfoxaflor. This approach will account for all chronic toxicity, including carcinogenicity that could result from exposure to sulfoxaflor. Chronic dietary risk estimates are below levels of concern; therefore, cancer risk is also below levels of concern.

There is a reasonable certainty that no harm will result to the general population, or to infants and children from aggregate exposure to sulfoxaflor as used in this emergency exemption request.

SECTION 166.20(a)(7): DISCUSSION OF RISK INFORMATION

Human Health Effects – Michael Hare, Ph.D.
Ecological Effects – David Villarreal, Ph.D.
Environmental Fate – David Villarreal, Ph.D.

Human Health

Toxicological Profile

Sulfoxaflor is a member of a new class of insecticides, the sulfoximines. It is an activator of the nicotinic acetylcholine receptor (nAChR) in insects and, to a lesser degree, mammals. The nervous system and liver are the target organs, resulting in developmental toxicity and hepatotoxicity.

Developmental toxicity was observed in rats only. Sulfoxaflor produced skeletal abnormalities likely resulting from skeletal muscle contraction due to activation of the skeletal muscle nAChR in utero. Contraction of the diaphragm, also related to skeletal muscle nAChR activation, prevented normal breathing in neonates and increased mortality. The skeletal abnormalities occurred at high doses while decreased neonatal survival occurred at slightly lower levels.

Sulfoxaflor and its major metabolites produced liver weight and enzyme changes, and tumors in subchronic, chronic and short-term studies. Hepatotoxicity occurred at lower doses in long-term studies compared to short-term studies.

Reproductive effects included an increase in Leydig cell tumors which were not treatment related due to the lack of dose response, the lack of statistical significance for the combined tumors, and the high background rates for this tumor type in F344 rats. The primary effects on male reproductive organs are secondary to the loss of normal testicular function due to the size of the Leydig Cell adenomas. The secondary effects to the male reproductive organs are also not treatment related. It appears that rats are uniquely sensitive to these developmental effects and are unlikely to be relevant to humans.

Clinical indications of neurotoxicity were observed at the highest dose tested in the acute neurotoxicity study in rats. Decreased motor activity was also observed in the mid- and high-dose groups. Since the neurotoxicity was observed only at a very high dose and many of the effects are not consistent with the perturbation of the nicotinic receptor system, it is unlikely that these effects are due to activation of the nAChR.

Tumors have been observed in rat and mouse studies. In rats, there were significant increases in hepatocellular adenomas in the high-dose males. In mice, there were significant increases in hepatocellular adenomas and carcinomas in high dose males. In female mice, there was an increase in carcinomas at the high dose. Liver tumors in mice were treatment-related. Leydig cell tumors were also observed in the high-dose group of male rats, but were not related to treatment. There was also a significant increase in preputial gland tumors in male rats in the high-dose group. Given that the liver tumors are produced by a non-linear mechanism, the Leydig cell tumors were not treatment-related, and the preputial gland tumors only occurred at the high dose in one sex of one species, the evidence of carcinogenicity was weak.

Ecological Toxicity

Sulfoxaflor (N-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-lambda 4-sulfanylidene]) is a new variety of insecticide as a member of the sulfoxamine subclass of neonicotinoid insecticides. It is considered an agonist of the nicotinic acetylcholine receptor and exhibits excitatory responses including tremors, followed by paralysis and mortality in target insects. Sulfoxaflor consists of two diastereomers in a ratio of approximately 50:50 with each diastereomer consisting of two enantiomers. Sulfoxaflor is systemically distributed in plants when applied. The chemical acts through both contact action and ingestion and provides both rapid knockdown (symptoms are typically observed within 1-2 hours of application) and residual control (generally provides from 7 to 21 days of residual control). Incident reports submitted to EPA since approximately 1994 have been tracked via the Incident Data System. Over the 2012 growing season, a Section 18 emergency use was granted for application of sulfoxaflor to cotton in four states (MS, LA, AR, TN). No incident reports have been received in association with the use of sulfoxaflor in this situation.

Sulfoxaflor is classified as practically non-toxic on an acute exposure basis, with 96-h LC_{50} values of >400 mg a.i./L for all three freshwater fish species tested (bluegill, rainbow trout, and common carp). Mortality was 5% or less at the highest test treatments in each of these studies. Treatment-related sublethal effects included discoloration at the highest treatment concentration (100% of fish at 400 mg a.i./L for bluegill) and fish swimming on the bottom (1 fish at 400 mg a.i./L for rainbow trout). No other treatment-related sublethal effects were reported. For an estuarine/marine sheepshead minnow, sulfoxaflor was also practically non-toxic with an LC_{50} of 288 mg a.i./L. Sublethal effects included loss of equilibrium or lying on the bottom of aquaria at 200 and 400 mg a.i./L. The primary degradate of sulfoxaflor is also classified as practically non-toxic to rainbow trout on an acute exposure basis (96-h LC_{50} >500 mg a.i./L).

Adverse effects from chronic exposure to sulfoxaflor were examined with two fish species (fathead minnow and sheepshead minnow) during early life stage toxicity tests. For fathead minnow, the 30-d NOAEC is 5 mg a.i./L based on a 30% reduction in mean fish weight relative to controls at the next highest concentration (LOAEC=10 mg a.i./L). No statistically significant and/or treatment-related effects were reported for hatching success, fry survival and length. For sheepshead minnow, the 30-d NOAEC is 1.3 mg a.i./L based on a statistically significant reduction in mean length (3% relative to controls) at 2.5 mg a.i./L. No statistically significant and/or treatment-related effects were reported for hatching success, fry survival and mean weight.

The acute toxicity of sulfoxaflor was evaluated for one freshwater invertebrate species, the water flea and two saltwater species (mysid shrimp and Eastern oyster). For the water flea, the 48-h EC_{50} is >400 mg a.i./L, the highest concentration tested. For Eastern oyster, new shell growth was significantly reduced at 120 mg a.i./L (75% reduction relative to control). The 96-h EC_{50} for shell growth is 93 mg a.i./L. No mortality occurred at any test concentration. Mysid shrimp are the most acutely sensitive invertebrate species tested with sulfoxaflor based on water column only exposures, with a 96-h LC_{50} of 0.67 mg a.i./L. The primary degradate of sulfoxaflor is also classified as practically non-toxic to the water flea (EC_{50} >240 mg a.i./L).

The chronic effects of sulfoxaflor to the water flea were determined in a semi-static system over a period of 21 days to nominal concentrations of 6.25, 12.5, 25, 50 and 100 mg a.i./L. Adult mortality, reproduction rate (number of young), length of the surviving adults, and days to first brood were used to determine the toxicity endpoints. No treatment-related effects on adult mortality or adult length were observed. The reproduction rate and days to first brood were significantly ($p<0.05$) different in the 100 mg a.i./L test group (40% reduction in mean number of offspring; 35% increase in time to first brood). No significant effects were observed on survival, growth or reproduction at the lower test concentrations. The 21-day NOAEC and LOAEC were determined to be 50 and 100 mg a.i./L, respectively.

The chronic effects of sulfoxaflor to mysid shrimp were determined in a flow-through system over a period of 28 days to nominal concentrations of 0.063, 0.13, 0.25, 0.50 and 1.0 mg a.i./L. Mortality of parent (F_0) and first generation (F_1), reproduction rate of F_0 (number of young), length of the surviving F_0 and F_1, and days to first brood by F_0 were used to determine the toxicity endpoints. Complete F_0 mortality (100%) was observed at the highest test concentration of 1.0 mg a.i./L within 7 days; no treatment-related effects on F_0/F_1 mortality, F_0 reproduction rate, or F_0/F_1 length were observed at the lower test concentrations. The 28-day NOAEC and LOAEC were determined to be 0.11 mg and 0.25 mg a.i./L, respectively.

Sulfoxaflor exhibited relatively low toxicity to aquatic non-vascular plants. The most sensitive aquatic nonvascular plant is the freshwater diatom with a 96-h EC_{50} of 81.2 mg a.i./L. Similarly, sulfoxaflor was not toxic to the freshwater vascular aquatic plant, *Lemna gibba*, up to the limit amount, as indicated by a 7-d EC_{50} for frond count, dry weight and growth rate of >100 mg a.i./L with no significant adverse effects on these endpoints observed at any treatment concentration.

Based on an acute oral LD_{50} of 676 mg a.i./kg bw for bobwhite quail, sulfoxaflor is considered slightly toxic to birds on an acute oral exposure basis. On a subacute, dietary exposure basis, sulfoxaflor is classified as practically nontoxic to birds, with 5-d LC_{50} values of >5620 mg/kg-diet for mallard ducks and bobwhite quail. The NOAEL from these studies is 5620 mg/kg-diet as no treatment related mortality of sublethal effects were observed at any treatment. Similarly, the primary degradate is classified as practically nontoxic to birds on an acute oral exposure basis with a LD_{50} of >2250 mg a.i./kg bw. In two chronic, avian reproductive toxicity studies, the 20-week NOAELs ranged from 200 mg/kg-diet (mallard, highest concentration tested) to 1000 mg/kg-diet (bobwhite quail, highest concentration tested). No treatment-related adverse effects were observed at any test treatment in these studies.

For bees, sulfoxaflor is classified as very highly toxic with acute oral and contact LD_{50} values of 0.05 and 0.13 µg a.i./bee, respectively, for adult honey bees. For larvae, a 7-d oral LD_{50} of >0.2 µg a.i./bee was determined (45% mortality occurred at the highest treatment of 0.2 µg a.i./bee). The primary metabolite of sulfoxaflor is practically non-toxic to the honey bee. This lack of toxicity is consistent with the cyano-substituted neonicotinoids where similar cleavage of the cyanide group appears to eliminate their insecticidal activity. The acute oral toxicity of sulfoxaflor to adult bumble bees (*Bombus terrestris*) is similar to the honey bee; whereas its acute contact toxicity is about 20X less toxic for the bumble bee. Sulfoxaflor did not demonstrate substantial residual toxicity to honey bees exposed via treated and aged alfalfa (i.e., mortality was <15% at maximum application rates).

At the application rates used (3-67% of US maximum), the direct effects of sulfoxaflor on adult forager bee mortality, flight activity and the occurrence of behavioral abnormalities is relatively short-lived, lasting 3 days or less. Direct effects are considered those that result directly from interception of spray droplets or dermal contact with foliar residues. The direct effect of sulfoxaflor on these measures at the maximum application rate in the US is presently not known. When compared to control hives, the effect of sulfoxaflor on honey bee colony strength when applied at 3-32% of the US maximum proposed rate was not apparent in most cases. When compared to hives prior to pesticide application, sulfoxaflor applied to cotton foliage up to the maximum rate proposed in the US resulted in no discernible decline in mean colony strength by 17 days after the first application. Longer-term results were not available from this study nor were concurrent controls included. For managed bees, the primary exposure routes of concern include direct contact with spray droplets, dermal contact with foliar residues, and ingestion through consumption of contaminated pollen, nectar and associated processed food provisions. Exposure of hive bees via contaminated wax is also possible. Exposure of bees through contaminated drinking water is not expected to be nearly as important as exposure through direct contact or pollen and nectar.

In summary, sulfoxaflor is slightly toxic to practically non-toxic to fish and freshwater water aquatic invertebrates on an acute exposure basis. It is also practically non-toxic to aquatic plants (vascular and non-vascular). Sulfoxaflor is highly toxic to saltwater invertebrates on an acute exposure basis. The high toxicity of sulfoxaflor to mysid shrimp and benthic aquatic insects relative to the water flea is consistent with the toxicity profile of other insecticides with similar MOAs. For birds and mammals, sulfoxaflor is classified as moderately toxic to practically non-toxic on an acute exposure basis. The threshold for chronic toxicity (NOAEL) to birds is 200 ppm and that for mammals is 100 ppm in the diet. Sulfoxaflor did not exhibit deleterious effects to terrestrial plants at or above its proposed maximum application rates.

For bees, sulfoxaflor is classified as very highly toxic. However, if this insecticide is strictly used as directed on the Section 18 supplemental label, no significant adverse effects are expected to Texas wildlife. Of course, standard precautions to avoid drift and runoff to waterways of the state are warranted. As stated on the Section 3 label, risk to managed bees and native pollinators from contact with pesticide spray or residues can be minimized when applications are made before 7 am or after 7 pm or when the temperature is below 55°F at the site of application.

Environmental Fate

Sulfoxaflor is a systemic insecticide which displays translaminar movement when applied to foliage. Movement of sulfoxaflor within the plant follows the direction of water transport within the plant (i.e., xylem mobile) as indicated by phosphor translocation studies in several plants. Sulfoxaflor is characterized by a water solubility ranging from 550 to 1,380 ppm. Sulfoxaflor has a low potential for volatilization from dry and wet surfaces (vapor pressure= 1.9×10^{-8} torr and Henry's Law constant= 1.2×10^{-11} atm m^3 $mole^{-1}$, respectively at 25 °C). Partitioning coefficient of sulfoxaflor from octanol to water (K_{ow} @ 20 C & pH 7= 6; Log K_{ow} = 0.802) suggests low potential for bioaccumulation. No fish bioconcentration study was provided due to the low K_{ow}, but sulfoxaflor is not expected to bioaccumulate in aquatic systems. Furthermore, sulfoxaflor is not expected to partition into the sediment due to low K_{oc} (7-74 mL/g).

Registrants tests indicate that hydrolysis, and both aqueous and soil photolysis are not expected to be important in sulfoxaflor dissipation in the natural environment. In a hydrolysis study, the parent was shown to be stable in acidic/neutral/alkaline sterilized aqueous buffered solutions (pH values of 5, 7 and 9). In addition, parent chemical as well as its major degradate, were shown to degrade relatively slowly by aqueous photolysis in sterile and natural pond water ($t^{½}$= 261 to >1,000 days). Furthermore, sulfoxaflor was stable to photolysis on soil surfaces. Sulfoxaflor is expected to biodegrade rapidly in aerobic soil (half-lives <1 day). Under aerobic aquatic conditions, biodegradation proceeded at a more moderate rate with half-lives ranging from 37 to 88 days. Under anaerobic soil conditions, the parent compound was metabolized with half-lives of 113 to 120 days while under anaerobic aquatic conditions the chemical was more persistent with half-lives of 103 to 382 days. In contrast to its short-lived parent, the major degradate is expected to be more persistent than its parent in aerobic/anaerobic aquatic systems and some aerobic soils. In other soils, less persistence is expected due to mineralization to CO_2 or the formation of other minor degradates.

In field studies, sulfoxaflor has shown similar vulnerability to aerobic bio-degradation in nine out of ten terrestrial field dissipation studies on bare-ground/cropped plots (half-lives were <2 days in nine cropped/bare soils in CA, FL, ND, ON and TX and was 8 days in one bare ground soil in TX). The chemical can be characterized by very high to high mobility (Kf_{oc} ranged from 11-72 mL g^{-1}). Rapid soil degradation is expected to limit chemical amounts that may potentially leach and contaminate ground water. Contamination of groundwater by sulfoxaflor will only be expected when excessive rain occurs within a short period (few days) of multiple applications in vulnerable sandy soils. Contamination of surface water by sulfoxaflor is expected to be mainly related to drift and very little due to run-off. This is because drifted sulfoxaflor that reaches aquatic systems is expected to persist while that reaching the soil system is expected to degrade quickly with slight chance for it to run-off.

When sulfoxaflor is applied foliarly on growing crops it is intercepted by the crop canopy. Data presented above appear to indicate that sulfoxaflor enters the plant and is incorporated in the plant foliage with only limited degradation. It appears that this is the main source of the insecticide sulfoxaflor that would kill sap sucking insects. This is because washed-off sulfoxaflor, that reaches the soil system, is expected to degrade.

In summary, sulfoxaflor has a low potential for volatilization from dry and wet surfaces. This chemical is characterized by a relatively higher water solubility. Partitioning coefficient of sulfoxaflor from octanol to water suggests low potential for bioaccumulation in aquatic organisms such as fish. Sulfoxaflor is resistant to hydrolysis and photolysis but transforms quickly in soils. In contrast, sulfoxaflor reaching aquatic systems by drift is expected to degrade rather slowly. Partitioning of sulfoxaflor to air is not expected to be important due to the low vapor pressure and Henry's Law constant for sulfoxaflor. Exposure in surface water results from drifted parent as only minor amounts is expected to run-off only when rainfall and/or irrigation immediately follow application. The use of this insecticide is not expected to significantly adversely impact Texas ecosystems with use according to the Section 18 label with this application. Of course, caution is needed to prevent exposure to water systems because of toxicity issues to aquatic invertebrates. As stated on the Section 3 label, this product should never be applied directly to water, to areas where surface water is present or to intertidal areas below the mean water mark. Do not contaminate water when disposing of equipment rinsates.

Endangered and Threatened Species in Oklahoma

No impacts are expected on endangered and threatened species by this very limited use of this insecticide as delineated in the Section 18 application. Sulfoxaflor demonstrates a very favorable ecotoxicity and fate profile as stated above and should not directly impact any protected mammal, fish, avian, or plant species. This product does adversely affect insects and aquatic invertebrates, especially bees, but the limited exposure to these species should not negatively affect endangered and threatened species in Oklahoma. As always, the label precautions need be strictly adhered to.

SECTION 166.20(a)(8): COORDINATION WITH OTHER AFFECTED STATE OR FEDERAL AGENCIES

The following state/federal agencies were notified of the Oklahoma Department of Agriculture, Food, and Forestry actions to submit an application for a specific exemption to EPA:

- Oklahoma Department of Environmental Quality (ODEQ), Air Quality Control
- Oklahoma Department of Environmental Quality (ODEQ), Water Quality
- Oklahoma Department of Health
- Oklahoma Department of Wildlife Conservation
- U.S. Fish and Wildlife Department

Responses from these agencies will be forwarded to EPA immediately if and when received by ODA.

SECTION 166.20(a)(9): ACKNOWLEDGEMENT BY THE REGISTRANT

Dow AgroScience has been notified of this agency's intent regarding this application (see attached letter of support). They have also provided a copy of a label with the use directions for this use (although this use is dependent upon the approval of this section-18 by EPA).

SECTION 166.20(a)(10): DESCRIPTION OF PROPOSED ENFORCEMENT PROGRAM

The State Legislature has endowed the ODAFF with the authority to regulate the distribution, storage, sale, use and disposal of pesticides in the state of Oklahoma. In addition, the EPA/ODAFF grant enforcement agreement provides the Department with the authority to enforce the provisions of the FIFRA, as amended, within the state. Therefore, the Department is not lacking in authority to enforce the provisions of an EPA approved specific exemption. If this specific exemption request is approved, ODAFF Pesticide Enforcement Specialists will make a number of random, unannounced calls on both growers and applicators to check for compliance with provisions of the specific exemption. If violations are discovered appropriate enforcement will be taken.

SECTION 166.20(a)(11): REPEAT USES

This is the second time Oklahoma Department of Agriculture, Food, & Forestry has applied for this specific exemption.

SECTION 166.20(b)(1): NAME OF THE PEST

Pseudatomoscelis seriatus, Cotton fleahopper (Reuter)
Lygus lineolaris (Palisot de Beauvois), Tarnished Plant Bug

SECTION 166.20(b)(2): DISCUSSION OF EVENTS OR CIRCUMSTANCES WHICH BROUGHT ABOUT THE EMERGENCY SITUATION

In 2018, producers harvested ca. 1.06 million bales of cotton on 550,000 acres in Oklahoma, worth about $362.3 million. Predictions for 2019 are for ca. 800,000 planted-acres of cotton. As acreage increases, so will the pressure from cotton fleahopper and tarnished plant bug, and other plant-sucking insects. Most currently registered products are either pyrethroids (IRAC class 3) or organophosphates (IRAC class 1B). Tarnished plant bug is a common insect pest of alfalfa in Oklahoma, where most of the new acres will be planted.

SECTION 166.20(b)(3): DISCUSSION OF ANTICIPATED RISKS TO ENDANGERED OR THREATENED SPECIES, BENIFICIAL ORGANISMS, OR THE ENVIRONMENT

As discussed previously, it is not anticipated that there should be any anticipated risks to endangered or threatened species, beneficial organisms or the environment if the application is made according to the section 18 use directions.

SECTION 166.20(b)(4): DISCUSSION OF SIGNIFICANT ECONOMIC LOSS

Plant bugs contributed to more than $10 million in yield loss to Oklhaoma cotton in 2017.

Dow AgroSciences

Dow AgroSciences LLC 9330 Zionsville Road Indianapolis, IN 46268-1054 USA

Transform® WG

EPA Reg. No: 62719-625

For Control of Plant Bugs in Cotton

Section 18 Emergency Exemption

File symbol: XXXXXX

FOR DISTRIBUTION AND USE ONLY IN OKLAHOMA UNDER SECTION 18 EMERGENCY EXEMPTION.

This Section 18 Emergency Exemption is effective XXXXX and expires XXXXX.

- This labeling must be in the possession of the user at the time of application.
- It is in violation of federal law to use this product in a manner inconsistent with its labeling.
- Read the label affixed to the container for Transform® WG insecticide before applying. Carefully follow all precautionary statements and applicable use directions.
- Any adverse effects resulting from the use of Transform WG under this emergency exemption must be immediately reported to the Oklahoma Department of Agriculture Food and Forestry.

Environmental Hazards Statement: This product is highly toxic to bees exposed through contact during spraying and while spray droplets are still wet. This product may be toxic to bees exposed to treated foliage for up to 3 hours following application. Toxicity is reduced when spray droplets are dry. Risks to managed and native pollinators from contact with pesticide spray or residues can be minimized when applications are made before 7:00 a.m. or after 7:00 p.m. local time or when the temperature is below 55 degrees Fahrenheit (°F) at the site of application.

Directions for Use

Pests and Application Rates:

Pests	Transform WG (fl. oz./acre)
Plant bugs	1.5 fl. oz. – 2.25 fl. oz. (0.047 – 0.071 lb ai/acre)

Advisory Pollinator Statement: Notifying known beekeepers within 1 mile of the treatment area 48 hours before the product is applied will allow them to take additional steps to protect bees. If known apiaries are within one mile of cotton fields intended for treatment, applications should be made before 7:00 a.m. or after 7:00 p.m. local time during the flowering period. Growers are advised to refer and, when feasible, observe the cooperative standards outlined in the Oklahoma Managed Pollinator Protection Plan for additional guidance and bee conservation stewardship efforts.

Application Timing: Treat in accordance with local economic thresholds. Consult your Dow AgroSciences representative, cooperative extension service, certified crop advisor or state agricultural experiment station for any additional local use recommendations for your area.

Application Rate: Use a higher rate in the rate range for heavy pest populations. Two applications may be required for optimum tarnished plant bug control under high pest pressure or heavy immigration of plant bugs from other crops.

Spray Drift Management: Applications are prohibited above wind speeds of 10 miles per hour (mph).

Restrictions:

- **Preharvest Interval:** Do not apply within 14 days of harvest.
- A restricted entry interval (REI) of 24 hours applies to all applications.
- **Minimum Treatment Interval:** Do not make applications less than 5 days apart.
- Do not make more than four applications per acre per year.
- Do not make more than two consecutive applications per crop.
- Do not apply more than a total of 8.5 fl. oz of Transform WG (0.266 lb ai of sulfoxaflor) per acre per year.

R396-239
Approved: __/__/__
Replaces R396-206

Status of Insecticide Resistance: Tarnished Plant Bug

Tarnished plant bug populations with resistance to pyrethroid insecticides high enough to cause control failures in the field were first found in the delta of Mississippi in 1993. Resistant populations had cross resistance to the different pyrethroids used in cotton and the resistance was metabolic and inherited as a recessive trait. Levels of resistance to pyrethroids varies from year to year because it is a recessive trait, but resistance is well established in most populations found in the delta of MS, the southeastern delta of AR, and in northeastern LA. Plant bug populations found in the "hill" region of MS, northeastern AR, and TN have average resistance levels lower than other areas of the mid-South, and susceptible populations can be frequently found. No tarnished plant bug populations with high levels of resistance to imidacloprid or thiamethoxam have been found in five years of testing in the mid-South. High levels of resistance to acephate were first found in a few locations in the mid-South in 2005. This resistance was widespread throughout the mid-South in the fall of 2006. Over 80% of all populations tested over the past five years had acephate resistance high enough to cause control problems with acephate in the field. The rapid spread of acephate resistance and its persistence in populations was due to the widespread use of acephate in cotton and the semi-dominant inheritance of the resistance gene(s). Tarnished plant bug populations are now commonly found in the mid-South with resistance to carbamate, organophosphate, and pyrethroid insecticides. Controlling these populations in cotton is difficult and frequently requires the use of novaluron for nymphs and combination treatments of two insecticides for nymphs and adults.

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Dow AgroSciences

November 10, 2010

Dr. B. Rogers Leonard
Professor of Entomology and
J. Hamilton Regents Chair in Cotton Production
Louisiana State University Agricultural Center
212A Macon Ridge Road
Winnsboro, LA 71295-5719

Dear Dr. Leonard,

Per your request, attached are copies of two scientific articles that have recently been accepted for publication:

Zhu et al., Discovery and characterization of sulfoxaflor, a new sap-feeding insecticide. For publication in *Journal of Agricultural and Food Chemistry*.

Babcock et al., Biological characterization of sulfoxaflor, a novel insecticide. For publication in *Pest Management Science*.

Both of these articles should appear in the respective journals in the near future. Until that time, per the conditions these journals have regarding prepublication, please consider these confidential information for use only by LSU, the State of Louisiana and the US Environmental Protection Agency in evaluating a potential Section 18 Registration for sulfoxaflor.

If you have questions, please do not hesitate to contact me.

Sincerely,

Jamey Thomas, Ph.D.
Global Biology Team Leader
Dow AgroSciences
317-337-4138

Pest Management Science

Biological Characterization of Sulfoxaflor, a Novel Insecticide

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Biological Characterization of Sulfoxaflor, a Novel Insecticide.

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ABSTRACT

BACKGROUND. The commercialization of new insecticides is important for ensuring that multiple effective product choices are available. In particular, new insecticides that exhibit high potency and lack insecticidal cross-resistance are particularly useful in insecticide resistance management (IRM) programs. Sulfoxaflor possesses these characteristics and is the first compound under development from the novel sulfoxamine class of insecticides.

RESULTS. In the laboratory, sulfoxaflor demonstrated high levels of insecticidal potency against a broad range of sap-feeding insect species. The potency of sulfoxaflor was comparable to commercial products, including neonicotinoids, for the control of a wide range of aphids and whiteflies (Homoptera), and true bugs (Heteroptera). Sulfoxaflor performed equally well in the laboratory against both insecticide-susceptible and -resistant populations of sweetpotato whitefly, *Bemisia tabaci* Gennadius and brown planthopper, *Nilaparvata lugens* (Stål), including populations resistant to the neonicotinoid insecticide imidacloprid. These laboratory efficacy trends were confirmed in field trials from multiple geographies, crops, and in populations of insects with histories of repeated exposure to insecticides. In particular, a sulfoxaflor use rate of 25 g ha^{-1} against cotton aphid (*Aphis gossypii* Glover) outperformed acetamiprid (25 g ha^{-1}) and dicrotophos (560 g ha^{-1}). Sulfoxaflor (50 g ha^{-1}) provided control of sweetpotato whitefly equivalent to acetamiprid (75 g ha^{-1}) and imidacloprid (50 g ha^{-1}) and better than thiamethoxam (50 g ha^{-1}).

CONCLUSION. The novel chemistry of sulfoxaflor, its unique biological spectrum of activity, and its lack of cross-resistance highlight the potential of sulfoxaflor as an important new tool for the control of sap-feeding insect pests.

Key Words: Sulfoxaflor, Sulfoximine, Discovery, Biology, Efficacy, insecticide, Heteroptera, Homoptera, IRM

Running head. Biological characteristics of sulfoxaflor

1 INTRODUCTION

Sap-feeding insects, primarily those from within the sub-orders Heteroptera and Homoptera, are among the most damaging crop pests based on annual global expenditures for their control. The resulting economic losses from sap-feeding insect damage often necessitate the use of intensive and diverse pest management approaches, including the use of insecticides. However, sap-feeding insects historically have been prone to the development of resistance to insecticides used for their control. Currently more than 1,350 reports of possible resistance from 80 different species of Homoptera and Hemiptera have been cataloged (Whalon ME, Mota-Sanchez D, Hollingworth RM and Duynslager L, http://www.pesticideresistance.org/). These reports of suspected sap-feeding insect resistance span a wide range of insecticide modes of action, including the neonicotinoid insecticides. This class of insecticides has been very widely used following the introduction of the first neonicotinoid insecticide, imidacloprid, nearly two decades ago.[1] Imidacloprid is currently the highest selling insecticide, and neonicotinoid insecticides collectively are the highest selling insecticide class, representing 24% of

global insecticide sales in 2007.[2] As with other insecticides, the widespread use of neonicotinoids such as imidacloprid has been accompanied by the development of resistance in insect populations, with the first documented report less than six years following the introduction of imidacloprid.[3] New incidences of resistance to imidacloprid and other neonicotinoid insecticides continue to be documented.[4, 5] Collectively, the high dependence on this class of insecticides and the increase in instances of resistance highlight a need for the development of insecticides effective against neonicotinoid-resistant insects.

The sulfoximines are a novel class of insecticides that are currently under evaluation by Dow AgroSciences (DAS) for the control of a broad range of sap-feeding insect pests.[6] Sulfoximines are unique among commercial insecticides because they all incorporate the sulfoximine functional group in their composition. Early discovery phase sulfoximine insecticides exhibited high levels of aphicidal activity in bioassays, which led to a more focused effort to maximize insecticidal potency and spectrum. Subsequent improvement in attributes resulted in the discovery of sulfoxaflor (Fig. 1), the first insecticide under development from the sulfoximine class of insecticides.[7] Although the insecticidal mode of action of sulfoxaflor is still under investigation, available data suggest that sulfoxaflor and closely related sulfoximine insecticides act through the activation of nicotinic acetylcholine receptors (nAChRs) (Watson GB, 2010, unpublished observations).

[Figure 1]

This report summarizes the potency and spectrum of activity of sulfoxaflor under laboratory and field conditions, and in reference to several commercially available insecticides from several insecticide chemistries. These results demonstrate the utility of

sulfoxaflor for the control of a range of insects, including those that are difficult to control due to resistance to currently registered insecticides.

2 MATERIALS AND METHODS

2. 1 Test materials

Technical materials were used for laboratory efficacy studies, and imidacloprid, thiamethoxam, acetamiprid, flonicamid, fipronil, spirotetramat and dinotefuran were obtained from ChemService Inc. (West Chester PA). Field trials were conducted using commercially available products; sulfoxaflor was prepared by DAS scientists as 100 or 240 g L^{-1} suspension concentrate (SC) formulations.

2.2 Laboratory bioassays.

2.2.1. Insecticide formulation.

Solutions were prepared in a similar manner for all assays except where noted. Insecticides were dissolved in organic solvent (acetone unless otherwise noted) to generate a concentrated stock solution which was further diluted with water. A range of at least 5 test concentrations was prepared by serial dilution with a mixture of the organic solvent and water solution appropriate for each assay. Insecticide solutions maintained a consistent ratio of solvent and water. A non-ionic surfactant (NIS) wetting agent was added in whole plant assays to all solutions. A sample of the solvent and water solution containing no insecticide was used as a solvent check in each assay.

2.2.2. Green peach aphid and cotton aphid.

Seedling cabbage (ca. 5 cm tall) or cotyledon stage squash plants were infested with approximately 25 apterous mixed-stage green peach aphid [GPA; *Myzus persicae* (Sulzer)] or cotton aphid (CA; *Aphis gossypii* Glover), respectively. One day after infestation, the plants were sprayed with insecticide solutions on all leaf surfaces using a hand-held aspirator sprayer. Insecticide solutions all contained 20% acetone+methanol (1+1 by volume) and were diluted with aqueous NIS (0.27 mg L^{-1}). Treated plants were held for 3 days (16:8 h light:dark photoperiod, 25°C), after which live aphids on each plant were counted. Aphids used in this study had been continuously reared for at least 5 years (GPA) and 3 years (CA) with no exposure to insecticides.

2.2.3. Sweetpotato whitefly.

Sweetpotato whitefly (DAS-WF-S; *Bemisia tabaci* Gennadius) adults were allowed to oviposit for 24–48 h on cotton, after which they were removed, leaving only eggs. At approximately 50% egg hatch, the cotton plants were sprayed on all leaf surfaces using a hand-held aspirator sprayer. Insecticide solutions all contained 20% acetone+ethanol (9+1 by volume) and aqueous NIS (0.54 mg L^{-1}). After 7 days (16:8 h light:dark photoperiod, 25°C), live nymphs and pupae were counted with the aid of a dissecting microscope. DAS-WF-S had been maintained without exposure to insecticides for at least 5 years.

2.2.4. Brown planthopper and green leafhopper.

Brown planthopper [BPH; *Nilaparvata lugens* (Stål)] used for systemic and foliar laboratory assays were originally field-collected in 1999 in Taiwan and have since been reared continuously in the lab without exposure to insecticides. Green leafhopper (GLH; *Nephotettix cincticeps* Uhler), also used for systemic and foliar lab evaluations, were

field-collected annually in Taiwan and colonized in the laboratory before use. Insecticide solutions contained 4% (systemic) and 10% (foliar) acetone in water. Five rice seedlings contained within a clear bioassay cylinder were treated by adding 25 mL of solution to the root zone (systemic assay) or by spraying with 0.5 mL of test solution using an aspirator sprayer (foliar assay). At least five laboratory reared 3rd-instar BPH or GLH were used for each within-bioassay replicate. Bioassay cylinders were held for 6 days (14:10 h light:dark photoperiod, 75% RH, 28°C), after which live nymphs were counted.

BPH collected in 2006 from a commercially managed rice field in Ogori, Japan, and subsequently maintained in the laboratory without exposure to insecticides were used to evaluate activity of sulfoxaflor via topical application. Insecticide activity was assessed by applying 0.08 µL of insecticide in acetone to the notum of each insect. Twelve to 18 BPH comprised one experimental unit and were held on rice for 1 day, after which BPH that were unresponsive were recorded as dead.

2.2.5. Western tarnished plant bug.

Western tarnished plant bugs (Lygus; *Lygus hesperus* Knight) were obtained from a laboratory culture that had had no exposure to insecticides for 5 years. Insecticide solutions all contained 5% acetone and aqueous NIS (0.27 mg L^{-1}). Green bean pod sections (2.5 cm) were submerged in test solutions for 15 s, air dried and then placed into 32-well trays (Bio Serv, Frenchtown NJ). Four- to 6-day-old nymphs were temporarily immobilized with CO_2, and two were placed gently into each well with a treated green bean section. After 3 days (16:8 h light:dark photoperiod, 22°C, 40% RH), mortality was assessed

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2.2.6. Southern corn rootworm.

The southern corn rootworm (SCRW; *Diabrotica undecimpunctata howardi* Barber) used for these assays had been reared in continuous laboratory culture for >5 years without exposure to insecticides (Crop Characteristics Inc.). Insecticide solutions contained 90% acetone in water and were applied to the surface of insect diet in 32-well trays (Bio Serv, Frenchtown NJ). A single first-stage larva was then transferred to each of the treated wells. Infested wells were covered to prevent larval escape, and mortality was evaluated after 5 days in darkness at 28°C.

2.2.7. Colorado potato beetle.

Insecticide-susceptible Colorado potato beetle [CPB; *Leptinotarsus decemlineata* (Say)] was obtained from the New Jersey Department of Agriculture. Insecticide solutions contained 5% acetone and aqueous NIS (0.54 mg L^{-1}). Small tomato plants (10–15 cm) were sprayed on all leaf surfaces using a hand-held aspirator sprayer. When the plants were dry, five 2^{nd}-instar CPB larvae were placed onto two leaves that were cut from each of four replicate plants. Larval mortality was evaluated after 3 days (16:8 h light:dark photoperiod, 25°C).

2.2.8. Fruit fly.

Fruit fly [*Drosophila melanogaster*_Meigan (Dm-Oregon)] was reared continuously in the laboratory with no exposure to insecticides. Insecticide solutions contained 66% acetone and 34% of an aqueous sucrose solution (100 g L^{-1}). Aliquots of these solutions were applied to the surface of agar, air dried, and a minimum of five adults that had been chilled to facilitate handling were caged on each treated unit. After 2 days (16:8 h

light:dark photoperiod, 22°C), percentage mortality was calculated by counting live and dead flies.

2.2.9. Yellow fever mosquito.

Yellow fever mosquito [*Aedes aegypti* (L.)] was laboratory reared without exposure to insecticides. Aliquots of insecticide solutions containing 5% acetone in water were transferred into 96-well micro-titer plates and air dried. First-instar larvae suspended in water were pipetted into the test wells, and larval mortality was measured after 3 days (16:8 h light:dark photoperiod, 22°C).

2.3 Assessment of cross resistance.

2.3.1. Sweetpotato Whitefly.

Insecticide resistant and susceptible populations were evaluated using an adult foliar contact assay (Anonymous, http://www.irac-online.org/documents/method12a.pdf). An insecticide resistant *B. tabaci* B-biotype population (PB-1) with a history of imidacloprid exposure and loss of sensitivity was isolated in 2006 from a southeastern US commercial greenhouse. This population has periodically been selected for continued resistance to imidacloprid while in culture at DAS. PB-1 responses to insecticide were compared to the insecticide susceptible DAS-WF-S population. Mortality was evaluated at 2 days after treatment (16:8 h light:dark photopeiod, 25°C).

2.3.2. Brown planthopper.

An insecticide susceptible population of BPH (MAFF-S) collected in 1999 was obtained from a public research institution in Nagasaki, Japan (Ministry of Agriculture, Forestry and Fisheries), where it had previously been shown to be sensitive to imidacloprid. A

population of BPH (Ogori-R) not controlled by commercial applications of imidacloprid was field-collected in 2009 in Ogori, Japan. Following colonization, both populations were reared in isolation without subsequent exposure to insecticides. Sensitivities to sulfoxaflor, imidacloprid, and fipronil were measured using the methodology described above for the BPH topical laboratory bioassay.

2.4. Field studies

Trials were conducted across broad geographies and multiple crops against field populations of CA and whitefly (*B. tabaci* or *B. argentifolii*) and were selected to exemplify the efficacy of sulfoxaflor. Small plot methodologies were used to evaluate a single backpack sprayer application of each treatment for CA and two applications in whitefly trials. Application volume was chosen to give uniform coverage of the crops and ranged from 110 L ha^{-1} (seedling cotton) to 1500 L ha^{-1} (mature cucumber). Crop and aphid trial locations were cotton (Greece, US), melon (France), cucumber (Greece), squash (Italy), and eggplant (Italy). Whitefly trial crops and locations were pepper (Spain, Mexico), cotton (Greece), and bean (Mexico). Treatments were replicated 3–4 times in each trial and were applied when pest populations in the crop were at or above action thresholds and increasing. Efficacy was rated at various time periods after application by counting the number of insects per leaf or leaflet (aphid and whitefly) or per cotton terminal (aphid only). Data were transformed to percentage control relative to that in the untreated control treatments. A total of 12 CA and 6 whitefly studies from 2009 are summarized. Whitefly data reported are from ratings following the second application.

2.5. Statistical analyses.

When precounts of insects were not taken (e.g., on plant assays), counts of insects at the end of the evaluation period were converted to percentage control using Abbott's formula.[8] Levels of control were averaged across replications within a trial for each treatment and these averages from the different trials used to calculate LD_{50} values. Exceptions were the analyses of BPH populations MAFF-S and Ogori-R, which were assayed only once, and the analyses of CPB activity for which the bioassays were repeated twice. For these exceptions, replication values were used to calculate LC_{50} values. Dose response analyses were performed using linear regression with log transformed rates and probit transformed responses.[9] LC_{50} values and associated 95% confidence intervals were used to support differences between insecticide responses for each species evaluated. LC_{50} ratios were used to generate compound specific quantitative estimates of resistance (resistance ratios, RR) between populations identified *a priori* for comparison. Accordingly, RR were generated for whitefly (PB1 and DA-WF-S) and BPH (MAFF-R and Ogori-S).

Bayesian analyses were used to fit beta distributions to the percentage control data from the field efficacy studies.[10] Differences in treatment variances could not be reduced to acceptable levels via transformations making analysis of variance techniques unreliable. Treatments were considered significantly different if 95% credible intervals did not overlap.[11]

3 RESULTS

3.1. Laboratory Bioassays.

Against laboratory populations of GPA, the potency of sulfoxaflor was similar to imidacloprid, thiamethoxam and acetamiprid and significantly greater than the potencies of dinotefuran, flonicamid and spirotetramat (Table 1). The same relationships were consistent for CA with the exception that sulfoxaflor was significantly more active than imidacloprid. Against whitefly, the efficacy of sulfoxaflor was equivalent to the efficacies of imidacloprid and spirotetramat (Table 2). However, acetamiprid, thiamethoxam and dinotefuran were significantly more potent than either imidacloprid or sulfoxaflor against whitefly. Flonicamid was relatively weak against whiteflies, producing less than 50% mortality at the highest rate tested (200 mg L^{-1}). The activity of sulfoxaflor against Lygus was comparable to activity of imidacloprid, acetamiprid, and dinotefuran, but less than the activity of thiamethoxam (Table 2). Flonicamid and spirotetramat were inactive against Lygus in these assays. Sulfoxaflor was comparable in efficacy to imidacloprid in BPH and GLH foliar, systemic, and topical (BPH only) assays (Table 3). Sulfoxaflor was significantly less active than imidacloprid, acetamiprid, dinotefuran, and thiamethoxam against fruit fly, mosquito, and SCRW; flonicamid and spirotetramat were inactive against these insects (Tables 4, 5). Against CPB, sulfoxaflor was significantly less active than imidacloprid (Table 5).

[Table 1]

[Table 2]

[Table 3]

[Table 4]

[Table 5]

3.2. Cross-resistance assessment.

The PB1 population was significantly resistant to imidacloprid relative to the susceptible DAS-WF-S population resulting in a resistance ratio (RR) of 870. The responses of these two populations to sulfoxaflor were not significantly different based on overlapping confidence limits (Table 6). The susceptible DAS-WF-S population was 14 times more susceptible to imidacloprid compared to sulfoxaflor, suggesting that against this susceptible population imidacloprid was intrinsically more active. Sulfoxaflor was significantly less potent than either imidacloprid or fipronil against the MAFF-S BPH population (Table 7). However, against the BPH Ogori-R population, sulfoxaflor was significantly more potent than imidacloprid and significantly less potent than fipronil (Table 7). When compared with the susceptible MAFF-R population, the Ogori-R population showed significant resistance to imidacloprid (438 RR) and fipronil (9.3 RR) but not to sulfoxaflor (Table 7).

[Table 6]

[Table 7]

3.3 Field studies

Sulfoxaflor provided significantly greater control of CA than acetamiprid and dicrotophos across all crops and evaluation times (Table 8). Sulfoxaflor at 25 g ha^{-1} provided levels of control similar to 50 g ha^{-1} of thiamethoxam at 2-3 and 4-6 days after application evaluation intervals, thiamethoxam provided significantly better control than sulfoxaflor 7–8 days after application.

[Table 8]

Against whitefly, evaluation intervals reported are in days after the second application (DAA2). Sulfoxaflor provided significantly greater control than equivalent

rates of imidacloprid 9–11 DAA2, with trends toward higher levels of control at 3, 7-8 and 12-16 DAA2. Sulfoxaflor was significantly more efficacious than thiamethoxam at 3, 7-8 and 9–11 DAA2 and equivalent in activity at 12-16 DAA2. Acetamiprid at 75 g ha^{-1} provided similar levels of control at 3 and 7-8 DAA2 and significantly better control than sulfoxaflor at 12–16 DAA2 (Table 9).

[Table 9]

4 DISCUSSION

4. 1 Laboratory Bioassays

The laboratory bioassay results for sulfoxaflor compared with a range of commercial insecticides illustrate some interesting trends. Of greatest practical importance is that sulfoxaflor has high potency against several sap-feeding insects. In particular, the activity of sulfoxaflor under laboratory conditions was equivalent or superior to the neonicotinoid insecticides currently registered for the control of cotton and green peach aphids. Additionally, sulfoxaflor was consistently more potent than spirotetramat, dinotefuran, and flonicamid against these same aphids. In laboratory assays against insecticide susceptible whitefly, sulfoxaflor, spirotetramat, and imidacloprid were equally potent. However, sulfoxaflor was less potent than acetamiprid, thiamethoxam and dinotefuran in studies that targeted insecticide susceptible whitefly eggs and crawler stage nymphs (Table 2). Similar to its activity against aphids, the potency of sulfoxaflor was comparable to the potency of imidacloprid against BPH and GLH (Table 3) and comparable to the potency of all of the neonicotinoids tested, except thiamethoxam, for the control of Lygus (Table 2). Flonicamid was inactive against whitefly, and both flonicamid and spirotetramat were inactive against Lygus.

In contrast to the results from sap-feeding insect assays, sulfoxaflor was much less active than neonicotinoid insecticides for the control of the SCRW and less active than imidacloprid against CPB. The lack of sulfoxaflor activity against CPB may reflect the inherent lack of sensitivity of the CPB central nervous system to sulfoxaflor compared to imidacloprid (G. Watson, unpublished observations). Fruit fly and mosquito were less sensitive to sulfoxaflor than the neonicotinoid insecticides tested. Spirotetramat and flonicamid had no activity against SCRW, fruit fly and mosquito and were not tested against CPB.

Collectively, these results highlight the potential for sulfoxaflor to be used to control a range of economically important sap feeding insect species at use rates that are similar or lower than for other products in the marketplace. Relative to these same compounds the spectrum of sulfoxaflor is intermediate between some of the more broad-spectrum materials (eg., imidacloprid, thiamethoxam) and more narrowly active compounds (eg., flonicamid, spirotetramat).

4.2 Cross-resistance evaluations

To date, resistance to neonicotinoids in whitefly is almost exclusively associated with enhanced monooxygenase activity, and this mechanism is suspected to be at work in the PB1 B-biotype population of whitefly.[12-15] Likewise, recent surveys of neonicotinoid resistance in populations of BPH in Asia also suggest that over-expression of monooxygenases is the primary mechanism conferring resistance to imidacloprid, although target site-based resistance has been documented in a laboratory selected strain.[14,15] Because metabolic mechanisms are most commonly responsible for

imidacloprid resistance in BPH, it is likely that this mechanism is responsible for imidacloprid resistance in the Ogori-R BPH population. Sulfoxaflor displayed no cross-resistance in strains of whitefly and BPH that were highly resistant to imidacloprid (Tables 6 and 7). As such, sulfoxaflor represents a potential rotation partner or alternative to neonicotinoids such as imidacloprid where resistance in sap-feeding insect pests is an increasing concern. Bioassay results from other comparisons of a susceptible and multiple insecticide resistant populations of *B. tabaci* also established a lack of cross-resistance between sulfoxaflor and profenofos, deltamethrin, and imidacloprid, as well as other neonicotinoid insecticides (Gorman K, Denholm I, 2009, pers. comm.). Thus, available data demonstrate that sulfoxaflor is effective against whitefly and BPH strains that are resistant to imidacloprid. The lack of cross-resistance suggests that sulfoxaflor is not susceptible to the same putative metabolic mechanisms, i.e., over-expression of monooxygenase enzymes, that seem to underlie imidacloprid resistance in these species. Further support of this hypothesis is provided from studies indicating that sulfoxaflor is stable *in vitro* to monooxygenases that readily metabolize imidacloprid (Hasler JM, pers. comm.).

4.3 Field trials

Field data for CA reflect the high level of activity observed in the field for sulfoxaflor against several aphids, including *Aphis*, *Myzus*, *Brevicoryne* and *Macrosiphum* species. Rates of 25 g ha^{-1} typically provided equivalent or better control of aphids than currently used products that were applied at higher rates. Sulfoxaflor also provided good control of whitefly relative to the neonicotinoid products imidacloprid and thiamethoxam. Resistance to neonicotinoids has been documented in *Bemisia spp.*, but these populations

were not tested for resistance, and we can only speculate that it may have played a role in reduced efficacy of some standard insecticides. Sulfoxaflor has also shown excellent control in field trials of other sap-feeding insects, including difficult-to-control true bugs such as *L. hesperus* and *L. lineolaris* (Palisot De Beauvois).[16,17]

5 CONCLUSIONS

Sulfoxaflor offers significant potential for the control of sap-feeding insects due to its high levels of efficacy in laboratory and field studies. It is the first product being developed from the sulfoximine class of insecticides, a novel class discovered at Dow AgroSciences. Sulfoxaflor is distinct from the neonicotinoid insecticides due to its unique insecticidal spectrum of activity. Sulfoxaflor is also highly effective against sap-feeding insects that are resistant to imidacloprid, and as such, offers a new tool for use in resistance management programs.

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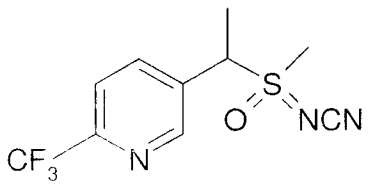

Figure 1. Sulfoxaflor. CAS. Reg. No. 946578-00-3. ((methyl(oxo) {1-[6-(trifluoromethyl)-3-pyridyl]ethyl}-λ^6-sulfanylidene)cyanamide. ISO 1750 (provisionally approved).

Table 1. Activity of sulfoxaflor compared with commercial sap-feeding insecticides for the control of green peach aphid and cotton aphid in laboratory bioassays.

	Green peach aphid[a]			Cotton aphid[b]		
	LC_{50} (95% CI)[c]	slope (± SE)	R^2	LC_{50} (95% CI)	Slope (± SE)	R^2
Sulfoxaflor	0.05 (0.02-0.09)	0.91(±0.12)	0.81	0.2 (0.015-1.1)	0.34(±0.04)	0.81
Imidacloprid	0.09 (0.07-0.13)	1.35(±0.12)	0.92	7.8 (2.4-15.6)	0.69(±0.13)	0.72
Acetamiprid	0.07 (0.03-0.12)	0.78(±0.01)	0.83	5.8(1.1-12.3)	1.0(±0.25)	0.67
Thiamethoxam	0.05 (0.03-0.08)	0.82(±0.08)	0.89	0.6 (0.09-0.2)	0.37(±0.04)	0.86
Dinotefuran	1.76 (0.87-4.48)	0.95(±0.16)	0.74	40 (30-60)	0.72(±0.05)	0.93
Flonicamid	0.76 (0.26-7.16)	0.49(±0.12)	0.55	80 (50-140)	0.39(±0.04)	0.84
Spirotetramat	0.26 (0.14-0.52)	0.81(±0.12)	0.78	770 (280-5110)	0.61(±0.14)	0.59

[a] mg L^{-1}

[b] µg L^{-1}

[c] Regression equations were all significant ($P< 0.05$)

Table 2. Activity of sulfoxaflor compared with commercial sap-feeding insecticides for the control of sweetpotato whitefly and western tarnished plant bug in laboratory bioassays.

	Sweetpotato whitefly[a]			Western tarnished plant bug[a]		
	LC_{50} (95% CI) [c]	slope (± SE)	R^2	LC_{50} (95% CI)	slope (± SE)	R^2
Sulfoxaflor	1.29 (0.76-2.08)	0.70(±0.07)	0.66	2.78 (1.41-4.95)	0.86(±0.09)	0.66
Imidacloprid	0.64 (0.32-1.11)	0.72(±0.09)	0.54	1.23 (0.48-2.61)	0.67(±0.11)	0.51
Acetamiprid	0.04 (0.02-0.08)	0.52(±0.06)	0.67	7.42 (2.73-30.47)	0.68(±0.17)	0.42
Thiamethoxam	0.20 (0.11-0.34)	0.63(±0.07)	0.61	0.09 (0.002-0.36)	0.60(±0.16)	0.39
Dinotefuran	0.13 (0.07-0.23)	0.70(±0.09)	0.72	4.95 (2.66-8.90)	1.42(±0.29)	0.61
Flonicamid	>200	NC[b]	NC	>200	NC	NC
Spirotetramat	1.47 (0.28-4.24)	0.85(±0.21)	0.56	>200	NC	NC

[a] mg L^{-1}

[b] Not calculated

[c] Regression equations were all significant ($P< 0.05$)

Table 3. Activity of sulfoxaflor compared with commercial sap-feeding insecticides for the control of brown planthopper and green leafhopper in laboratory bioassays.

	Brown planthopper			Green leafhopper		
	LC_{50} (95% CI)[c]	slope (± SE)	R^2	LC_{50} (95% CI)	slope (± SE)	R^2
	Foliar[a]			**Foliar**[a]		
Sulfoxaflor	0.16 (0.03-0.43)	0.84(±0.12)	0.93	0.05 (0.01-0.16)	0.65(±0.10)	0.93
Imidacloprid	0.12 (0.07-0.42)	1.89(±0.44)	0.9	0.05 (0.02-0.08)	2.13(±0.30)	0.96
	Systemic[a]			**Systemic**[a]		
Sulfoxaflor	0.04 (0-0.22)	0.53(±0.14)	0.77	0.07 (0-3.48)	0.65(±0.18)	0.75
Imidacloprid	0.50 (0.07-0.98)	1.91(±0.36)	0.93	0.29 (0.03-0.52)	1.85(±0.44)	0.89
	Topical[d]					
Sulfoxaflor	0.18 (0.13 - 0.28)	1.89(±0.31)	0.66	NT[b]		
Imidacloprid	0.11 (0.05 - 0.22)	0.86(±0.16)	0.66	NT[b]		

[a] mg L^{-1}

[b] Not tested

[c] Regression equations were all significant ($P< 0.055$)

[d] µg g^{-1} BPH live weight

Table 4. Activity of sulfoxaflor compared with commercial sap-feeding insecticides for the control of adult fruit fly and larval yellow fever mosquito in laboratory bioassays.

	Fruit fly[a]			Yellow fever mosquito[b]		
	LC_{50} (95% CI) [c]	slope (± SE)	R^2	LC_{50} (95% CI)	slope (± SE)	R^2
Sulfoxaflor	33.3 (14.86-96.54)	0.43(±0.05)	0.63	1.37 (0.64-4.31)	1.27(±0.26)	0.71
Imidacloprid	4.24 (2.68-7.03)	0.56(±0.04)	0.79	0.03 (0.01-0.04)	1.77(±0.31)	0.76
Acetamiprid	2.6 (1.92-3.57)	1.07(±-0.08)	0.93	0.06 (0.04-0.079)	2.71(±0.38)	0.83
Thiamethoxam	1.22 (0.59-2.15)	0.99(±0.13)	0.82	0.01 (0.004-0.01)	1.92(±0.34)	0.77
Dinotefuran	1.29 (0.56-2.34)	0.71(±0.07)	0.87	0.11 (0.09-0.13)	2.81(±0.29)	0.9
Flonicamid	>200	NC[d]		>174	NC	
Spirotetramat	>200	NC		>174	NC	

[a] $\mu g\ cm^{-1}$

[b] $mg\ L^{-1}$

[c] Regression equations were all significant ($P < 0.05$)

[d] Not calculated

Table 5. Activity of sulfoxaflor compared with commercial insecticides for the control of southern corn rootworm and Colorado potato beetle in laboratory bioassays.

	Southern corn rootworm[a]			Colorado potato beetle[b]		
	LC_{50} (95% CI)[c]	slope (± SE)	R^2	LC_{50} (95% CI)	slope (± SE)	R^2
Sulfoxaflor	2.01 (1.15-3.50)	0.78(±0.0.09)	0.66	52.04 (28.55-110.62)	0.80(±0.11)	0.88
Imidacloprid	0.07 (0.04-0.12)	0.87(±0.11)	0.68	0.39 (0.14-0.90)	0.77(±0.11)	0.87
Acetamiprid	0.02 (0.01-0.04)	0.67(±0.08)	0.83	NT[e]		
Thiamethoxam	0.03 (0.01-0.05)	0.72(±0.09)	0.83	NT		
Dinotefuran	0.32 (0.08-0.73)	0.63(±0.09)	0.77	NT		
Flonicamid	>200	NC[d]	NC	NT		
Spirotetramat	>200	NC	NC	NT		

[a] $\mu g\ cm^{-1}$

[b] $mg\ L^{-1}$

[c] Regression equations were all significant ($P< 0.05$)

[d] Not calculated

[e] Not Tested

Table 6. Insecticidal efficacy against imidacloprid-resistant (PB1) and -susceptible (DAS-WF-S) adult *Bemisia tabaci* in foliar contact/ingestion assays.

	DAS-WF-S[a]			PB1[a]			
	LC_{50} (95% CI)[b]	Slope (± SE)	R^2	LC_{50} (95% CI)	Slope (± SE)	R^2	RR_{LC50}[c]
Sulfoxaflor	2.8 (1.2-5.5)	0.51 (±0.04)	0.83	6.4 (2.6-13.1)	0.48(±0.05)	0.77	2.3
Imidacloprid	0.20 (0.05-0.55)	0.32 (±0.04)	0.76	174 (24.6->2000)	0.12(±0.03)	0.33	870

[a] mg L^{-1}

[b] Regression equations were all significant ($P < 0.05$)

[c] Resistance ratio

519 **Table 7.** Insecticidal efficacy against imidacloprid-susceptible (MAFF-S) and -resistant (Ogori-R) brown planthopper *(Niloparvata*

520 *lugens)* strains using a topical bioassay.

	MAFF-S[a]			Ogori-R[a]			
	LC_{50} (95% CI)[b]	Slope (± SE)	R^2	LC_{50} (95% CI)	Slope (± SE)	R^2	RR_{LC50}[c]
Sulfoxaflor	0.56 (0.41-0.73)	1.14(±0.12)	0.78	0.83 (0.63-1.12)	1.12(±0.12)	0.78	1.5
Imidacloprid	0.02 (0.01-0.03)	0.67(±0.06)	0.82	8.75 (4.93-18.3)	0.63(±0.07)	0.8	438
Fipronil	0.03 (0.02-0.04)	1.00(±0.14)	0.68	0.28 (0.21-0.37)	1.56(±0.17)	0.77	9.3

521

522 [a] $\mu g\ g^{-1}$ BPH live weight

523 [b] Regression equations were all significant ($P< 0.05$)

524 [c] Resistance ratio

Table 8. Summary of 12 cotton aphid (*Aphis gossypii*) field trials comparing sulfoxaflor with commercial standard insecticides.

		% Control, Days After Application[a]			
	Rate (g ha^{-1})	2-3	4-6	7-8	12-16
Sulfoxaflor	25	84	84	87	62
Acetamiprid	25	57 (-)		59 (-)	11 (-)
Thiamethoxam	50	81	79	99 (+)	
Dicrotophos	560	48 (-)	50 (-)		

[a] (-) indicates significantly decreased or significantly improved (+) control relative to sulfoxaflor based on 95% credible intervals.

529 **Table 9.** Summary of six whitefly (*Bemisia spp.*) field trials comparing sulfoxaflor with commercial standard insecticides.

		% Control, Days After Application Two[a]			
	Rate (g ha^{-1})	3	7-8	9-11	12-16
Sulfoxaflor	50	61	69	87	61
Acetamiprid	75	58	66		77 (+)
Imidacloprid	50	38	56	40 (-)	52
Thiamethoxam	50	31 (-)	39 (-)	40 (-)	49

530

531 [a] (-) indicates significantly decreased or significantly improved (+) control relative to sulfoxaflor based on 95% credible interval

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November 10, 2010

Dr. B. Rogers Leonard
Professor of Entomology and
J. Hamilton Regents Chair in Cotton Production
Louisiana State University Agricultural Center
212A Macon Ridge Road
Winnsboro, LA 71295-5719

Dear Dr. Leonard,

Per your request, attached are copies of two scientific articles that have recently been accepted for publication:

Zhu et al., Discovery and characterization of sulfoxaflor, a new sap-feeding insecticide. For publication in *Journal of Agricultural and Food Chemistry*.

Babcock et al., Biological characterization of sulfoxaflor, a novel insecticide. For publication in *Pest Management Science*.

Both of these articles should appear in the respective journals in the near future. Until that time, per the conditions these journals have regarding prepublication, please consider these confidential information for use only by LSU, the State of Louisiana and the US Environmental Protection Agency in evaluating a potential Section 18 Registration for sulfoxaflor.

If you have questions, please do not hesitate to contact me.

Sincerely,

Jamey Thomas, Ph.D.
Global Biology Team Leader
Dow AgroSciences
317-337-4138

Discovery and characterization of sulfoxaflor, a new sap-feeding insecticide

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For: Journal of Agriculture and Food Chemistry

Discovery and Characterization of Sulfoxaflor, A Novel Sap-Feeding Insecticide**

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ABSTRACT

The discovery of sulfoxaflor [*N*-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-λ^4-sulfanylidene] cyanamide] resulted from an investigation of the sulfoximine functional group as a novel bioactive scaffold for insecticidal activity and a subsequent extensive SAR study. Sulfoxaflor, the first product from this new class (the sulfoximines) of insect control agents, exhibits broad-spectrum efficacy against many sap-feeding insect pests, including aphids, whiteflies, hoppers, and *Lygus*, with levels of activity that are comparable to other classes of insecticides targeting sap-feeding insects, including the neonicotinoids. However, no cross-resistance has been observed between sulfoxaflor and neonicotinoids such as imidacloprid, apparently the result of differences in susceptibility to oxidative metabolism. Available data are consistent with sulfoxaflor acting via the insect nicotinic receptor in a complex manner. These observations reflect the unique structure of the sulfoximines compared with neonicotinoids.

Key Words
Nicotinic acetylcholine receptor, sulfoximines, sulfoxaflor, insecticide resistance, *Myzus persicae*

INTRODUCTION

Crop damage due to sap-feeding insects such as aphids and whiteflies can be extensive. Over time, there have been several classes of insecticides with different modes of action that have proven effective in the control of many sap-feeding pests. However, resistance to many of these insecticides has limited their utility (*1,2*). In fact, three of the ten species of insects that have developed resistance to the largest number of insecticides are sap-feeding insects (*1*). These three sap-feeding insects, *Myzus persicae* (green peach aphid), *Aphis gossypii* (cotton aphid), and *Bemisia tabaci* (sweet potato whitefly) have developed resistance to a variety of organophosphate, carbamate, pyrethroid and in some cases, neonicotinoid insecticides (*2-6*). Given the continuing development of insecticide resistance, there is an ongoing need for new insect control agents to provide effective control options for sap-feeding insect pests.

The discovery and development of new insect control agents can involve a wide variety of approaches including investigations of structural chemical scaffolds. Structural chemical scaffolds of interest, also known as privileged structures, can be associated with a certain type of biological activity, or may involve a key molecular fragment or recognition element known or suspected to be essential for the activity of a compound or ligand (*7-9*). Alternatively, privileged structures or scaffolds may simply be novel or underexplored chemical moieties with desired chemical or physical properties. As such, these privileged structures or scaffolds can be used as the basis for the design and synthesis of desired target sets of compounds that incorporate additional structural features such as putative carrier groups or binding elements.

Enticed by the potential of a scaffold-based approach for the generation of new chemistries, we initiated an effort to identify novel scaffolds for the development of novel crop protection agents. Candidate scaffolds included those that were small molecular weight entities, that possessed either a hydrogen bond donor and/or acceptor, that were novel or underexplored as agrochemicals, and those that were amenable to synthetic modification.

One structural scaffold selected for investigation was the sulfoximine functionality (Figure 1). Although sulfoximines have been reported in the literature as early as the 1940's (*10-13*) they have not been extensively examined for use as agrochemicals. Sulfoximines have a small hydrophilic core, a hydrogen bond acceptor and, in cases where R3 = H, hydrogen bond donor. They are also amenable to synthetic modifications since they possess, unlike the closely related sulfone, a third point of diversity at the imine nitrogen. These chemical characteristics made the sulfoximine functionality an appealing structural scaffold for further exploration.

DISCOVERY OF SULFOXIMINE INSECTICIDES

Several different sets of substituted sulfoximine scaffolds were initially prepared with a relatively diverse array of R1, R2, and R3 substituents. Selection of substituents was guided by agrochemical-like parameters (*14*) working within the framework of available substituents and known synthetic methods. Synthetic efforts evolved from a broad search for entities with agrochemical utility to a more focused exploration of structural motifs thought to be associated with fungicidal activity such as the aryloxybenzyl sulfoximines (Figure 2, structure **A**). In the course of exploring various

R3 substituents for the aryloxybenzyl sulfoximine series, an *N*-nitro sulfoximine was prepared using a literature method (*15*). Recognizing the method might provide access to a broader set of N-nitro sulfoximines, the motif was targeted for follow-up as a second generation structural scaffold (Figure 2, structure **B**). Further investigation of this structural scaffold eventually resulted in the synthesis and identification of the N-nitro sulfoximine **1**, which was found to have promising aphicidal activity (Figure 2). Sulfoximine **1** therefore represented a novel starting point for the optimization of the aphicidal activity.

The structure activity relationship (SAR) investigation of sulfoximine **1** was greatly enabled by two synthetic routes, both shown in Figure 3. The first synthetic route (Route A) is an adaptation of a procedure described by Johnson *et al.* where sulfoxides are functionalized with sodium azide and concentrated sulfuric acid to give unsubstituted sulfoximines (*16*). Subsequent nitration or cyanation provided targeted *N*-substituted sulfoximines (*15,17*). A scalable route was subsequently identified in which the oxidation steps of Route A are reversed, and the mild oxidant iodobenzene diacetate (*18*) is employed in the oxidative addition of cyanamide to disubstituted sulfides yielding *N*-cyano sulfilimines (Figure 3, Route B). Subsequent oxidation of the intermediate sulfilimine gave targeted *N*-cyano sulfoximine analogs. Decyanation via treatment with trifluoroacetic anhydride followed by basic hydrolysis (*19*) provided access to the unsubstituted sulfoximine, a key intermediate in the exploration of different imine substituents.

These two general routes enabled the synthesis of a number of molecules that helped define the sulfoximine SAR, particularly related to a wide range of different

substituents for both the imine nitrogen and the bridging methylene carbon linking the sulfoximine moiety to the pyridine ring. From this SAR, a compound with even greater aphicidal potency, the mono-methyl substituted, *N*-cyano sulfoximine **2** was identified (Figure 4).

DISCOVERY OF SULFOXAFLOR

From sulfoximine **2,** the effects of various modifications to the bridging methylene carbon linking the sulfoximine functionality and the pyridine ring were explored. Included in this investigation were various ring systems that conformationally biased the orientation of the sulfoximine functionality relative to the pyridine ring. These modifications employed a diverse set of synthetic schemes that allowed the synthesis of a variety of chemical targets (*17,20*). Emerging from these efforts was the observation that potent aphicidal activity tended to coincide with systems that employed a single methylene linker between the sulfoximine and the pyridyl ring, and a mono-substitution, preferably a methyl group, in an open chain form.

An investigation of pyridyl ring SAR revealed that the better aphicidal activity was afforded by small, lipophilic, electron-withdrawing substituents at the 6-position, with 6-triflouromethyl being one of the best substituents in terms of aphid control (*21,22*). The combination of the best features from these investigations, namely the *N*-cyano substitution, with a single mono-methyl-substituted methylene linker, and 6-triflouromethyl substitution on the pyridine ring, led to the discovery of sulfoxaflor (Figure 5). Sulfoxaflor was found to exhibit significantly better *M. persicae* activity than any other sulfoximine that had been prepared in the series. Below are brief descriptions

of studies characterizing the insecticidal activity, the cross-resistance to known resistant insects, and the mode of action of sulfoxaflor. In total, the data indicate that sulfoxaflor represents a novel sap-feeding insecticide with unique resistance and mode of action characteristics.

MATERIALS AND METHODS

Chemicals

All chemicals were from conventional sources. Sulfoxaflor, sulfoximine 1 and sulfoximine **2** were prepared at Dow AgroSciences. Imidacloprid (IMI) and acetamiprid, was purchased from Chem Service (West Chester, PA). [^{3}H] Imidacloprid ([^{3}H] IMI) was obtained from Amersham (Piscataway, NJ; specific activity37.2 Ci/mmol).

Laboratory bioassays

Laboratory leaf disk bioassays for Rothamsted susceptible and resistant strains of *M. persicae and B. tabaci* (See Table 1) were conducted as described previously (*23*). Bioassays of DAS strains of these same two species along with *A. gossypii* utilized whole plant bioassays as described previously (*24*). Laboratory bioassays for *Lygus hesperus* (tarnished plant bug) on green beans were also conducted as described previously (*24*).

UV Stability and Residual

Suspension concentrate (SC) formulations (1000 ppm) of sulfoxaflor and imidacloprid were applied to glass disks (10 µl / disk) held in a UV chamber for selected time intervals, extracted (acetonitile), and then analyzed by HPLC (Beckman Coulter, Brea CA, model 126, with a model 508 autosampler, and a model 168 photodiode array

detector set at 270 nm) using a Gemini (Phenomenex, Torrence, CA) 5 μm, C6-phenyl column; water:acetonitrile, 10%-100% gradient, 2 ml/min. There were three replicates per time point for each compound.

Sulfoxaflor and imidacloprid (25 g/ha each; 125 ppm) were applied to young pepper plants, allowed to dry, and then held in a UV chamber for selected time intervals. At each interval, the plants were infested with a mixed population of *M. persicae* and then assessed for *M. persicae* control three days later. There were four replicates per treatment / time point.

[^{3}H] imidacloprid binding assays

Myzus persicae were collected from leaf surfaces and frozen at -80° C. Frozen *M. persicae* were placed in chilled homogenization buffer (200 mM sucrose, 50 mM Trizma-HCl, 1 mM ethylenediaminetetraacetic acid, and 0.1 mM phenylmethanesulphonyl-fluoride, pH 7.2) and then homogenized using a cold (4° C) blender. The homogenized mixture was then filtered through cheesecloth to remove large debris. The resulting effluent was then centrifuged at 3500 rpm for fifteen minutes at 4° C. The supernatant was collected and subjected to an additional centrifugation at 17500 rpm for twenty minutes at 4° C. The supernatant was then discarded and the remaining pellet of tissue was resuspended in binding buffer (120 mM NaCl, 50 mM Trizma HCl, pH 7.4). The resulting protein preparation was aliquoted and frozen at -80° C.

Radioligand binding assays were performed in 96-well microtiter plates, at a final assay volume of 0.1 ml. For each replicate, ~ 2 nM [^{3}H] imidacloprid (IMI), protein (70 μg/well), and any unlabeled competing compound were co-incubated for 60 minutes at room temperature (~22° C). The binding reaction was initiated by the addition of protein

and terminated by filtration using a TomTec Mach-II harvester (TomTec, Inc., Hampden, CT). Filter mats were dried in an oven, and solid scintillant was then melted onto the filter. Bound radioactivity was counted using a Wallac 1453 Microbeta Plus scintillation counter (Wallac/Perkin Elmer, Waltham, MA). Total binding (in the absence of competing ligand), filter binding (in the absence of competing ligand and protein), and the binding of a positive control (i.e., unlabeled imidacloprid, unlabeled sulfoxaflor) were determined for each set of experiments. The resulting displacement data were fit by least squares non-linear regression using GraphPad Prism software (GraphPad Software, Inc., La Jolla, CA) and, when applicable, expressed as the concentration producing half-maximal displacement (IC_{50}, in nM).

Cloning of nicotinic acetylcholine receptor (nAChR) subunits and cRNA synthesis

The *D. melanogaster* α2 nAChR subunit (*Dα2*) was amplified from 1st strand cDNA made from *D, melanogaster* embryo mRNA (Clontech Laboratories, Mountain View, CA) using the primers SADFW2 (5' AGATCTCACCATGGCTCCTGGCTGCTGCAC 3') and SADRV2 (5' AGATCTTTAATTCTTCTTCTCGGTTA 3'). PCR was performed using the FailSafe PCR kit (Epicentre Biotechnologies, Madison, WI). A clone having a sequence similar to GenBank accession number X53583 was identified. The clone had a two conservative single base changes compared to the published sequence. This clone was isolated as a Bgl II fragment and ligated into pGH19. A clone having the *Dα2* gene in the correct orientation was identified by restriction digest.

The chicken β2 (β2) nAChR subunit was amplified from 1st strand cDNA made from chicken brain mRNA obtained from Clontech Laboratories, Inc. (Mountain View, CA). PCR was performed with the TaKaRa EX taq kit (TaKaRa Bio, Inc, Otsu, Japan) using the primers 5' GGATCCACGGACACGGAGGAGCGCCTGGTGGAATACCT 3'and 5' GGATCCCTATTTGGAGGTGGGGGTGCCCTGGCCGA 3'. This amplified the coding region for β2 without the signal peptide, and resulted in a product of 1434 bp which was cloned into pCR2.1-TOPO for sequencing. A clone having the β2 sequence corresponding to GenBank accession number AJ250362 was identified. The clone was amplified with the primer CK β2FL (5'GGATCCATGGCGCTGCTCCGCGTCCTCTGC CTCCTCGCCGCGCTCCGACGCAGTCTGTGCACGGACACGGAGGAGCGCCTG GTGGAATAC 3') to add the signal peptide sequence. The PCR product (1488 bp) was cloned into pCR2.1-TOPO and sequenced. A clone with the correct sequence was identified and the full length *β2* gene was removed as a Bam HI fragment and cloned into pGH19 (received from Cambria Biosciences, Boston, MA). A clone of pGH19/*CKβ2FL* was identified by restriction digest having the *CKβ2FL* gene in the correct orientation.

For cRNA synthesis, pGH19/ CKβ2FL was linearized with Nhe I and pGH19/Dα2 was linearized with Xho I. cRNA synthesis was carried out using the mMessage mMachine T7 Ultra kit (Ambion, Inc., Austin, TX). cRNAs were LiCl-precipitated and the pellets were redissolved (typically at 1 ng/nl) in "The RNA Storage Solution" (Ambion, Inc., Austin, TX) and the solution was stored at -80°C until thawed for injection into *X. leavis* oocytes.

Xenopus laevis oocyte preparation, expression, and electrophysiology

Gravid adult female *X. laevis* frogs were purchased from Nasco, Inc. (Fort Atkinson, WI) and maintained in dechlorinated water at room temperature. For oocyte removal, frogs were anesthetized by placing them in a water bath containing 0.2% tricaine methane sulfonate (pH 7.0) for 30 minutes. Following ovarectomy, harvested oocytes were placed in ND-96 medium (containing in mM: 96 NaCl, 2 KCl, 1.8 $CaCl_2$, 1 $MgCl_2$, 5 HEPES, pH 7.6) supplemented with 10,000 units/l penicillin, 10 mg/ml streptomycin, and 2.5 mM Na-pyruvate. Oocytes were then defolliculated by a 2 hour treatment with 1.5 mg/ml type 1A collagenase (Sigma Chemical, St. Louis, MO) in ND-96 medium without calcium. After defolliculation, oocytes were washed for 30 minutes in zero calcium ND-96 medium without collagenase, and then returned to standard ND-96 medium with calcium.

Stage V-VI oocytes were injected with individual, or mixtures of cRNAs encoding *D. melanogaster* nicotinic receptor subunits and the *C. elegans* chaperone protein ric-3. Each oocyte was injected with no more than 50 nl (1 ng/nl) total volume cRNA using a Nanoject II microinjector (Drummond Scientific, Broomall, PA). Oocytes were housed individually in 96-well plates in ND-96 medium and stored in an incubator maintained at 18° C. Oocytes were assayed for receptor expression 1-4 days after cRNA injection.

Electrophysiological recordings were performed using the Roboocyte automated oocyte recording system (Multichannel Systems, Reutlingen, Germany). Modified Barth's Saline (containing in mM: 88 NaCl, 2.4 $NaHCO_3$ 1 KCl, 0.41 $CaCl_2$, 0.3 $Ca(NO_3)_2$, 0.82 $MgSO_4$, 15 HEPES, pH 7.6) was used for all experiments. Oocytes were voltage-clamped to -60 mV with leak currents less than 1000 nA.. Responses to nAChR

agonists were measured at peak amplitude. Test compounds were first dissolved in DMSO at a high concentration and then diluted into MBS at the appropriate test concentration, with final DMSO levels never exceeding 0.1%. For dose-response studies, a 10 second application of 10 μM acetylcholine (ACh) was first applied to each oocyte, and then subsequent concentrations of test compounds were applied to oocytes at 10 minute intervals, beginning with the highest tested dose (100 μM). The resulting data were expressed as % of the initial response to ACh.

CYP6G1-mediated metabolism in D.mel-2 cells

The *CYP6G1* gene was amplified from adult *D. melanogaster* 1st strand cDNA. The primers added Bam HI sites to both ends of the gene and a 6X-His tag to the C-terminus. A product of 1608 bp was generated and ligated into pCR2.1-TOPO. Several clones containing the *CYP6G1* product were identified and sequenced. One sequence was found to match that of NCBI accession # NM136899 except for 4 single base changes which did not affect the amino acids at those positions and the 6X-His tag. For expression in *D. melanogaster* D. mel-2 cells, the *CYP6G1* was amplified by PCR using primers to change the Bam HI sites to Kpn I sites for subcloning into pAc5.1/V5-HisA. The PCR product was ligated into pCR2.1-TOPO and sequenced to insure no changes were introduced except the change in restriction sites. A clone was digested with Kpn I to isolate the CYP6G1, which was subsequently ligated into the pAc5.1/V5-HisA vector (Invitrogen). A clone containing the *CYP6G1* gene in the correct orientation was scaled up for plasmid isolation.

For transient expression, D.mel-2 cells were seeded 24 hours prior to transfection in 12 well plates (5 x 10^5 cells/well) and incubated at 27°C. A transfection mix containing 2 µg DNA and 8 µl Cellfectin (100 µl total volume) per well. A time course study indicated maximal CYP6G1 expression at 48 hours after transfection. Following 24 hr incubation, imidacloprid, acetamiprid or sulfoxaflor (400 ppm in water; filter sterilized (0.33 µm)) were added to the cells and then harvested at 0 and 48 hours after application of compound. At harvest time points, each well was scraped twice and the extracts were transferred to Eppendorf tubes where they were diluted with acetonitrile (CH_3CN, 450 µl total volume). HPLC (Agilent 1100 system, Agilent Technologies, Santa Clara, CA) analysis was carried out using a YMC J' Sphere ODS-H80, 150mm X 4.6mm column, (YMC Co. Kyoto, Japan) with UV detector set at 254nm. For imidacloprid and acetamiprid, the HPLC employed a gradient from 50% CH_3CN to 100% in 10 minutes at a flow rate of 1ml/min using 1%AA in water phase. For sulfoxaflor the HPLC employed a gradient from 50% CH_3CN to 100% in 5 minutes at a flow rate of 1ml/min using 1%AA in water phase. The D.mel-2 extracts were evaluated by LC- MS (Agilent Technologies, Santa Clara, CA) with detection of extracted ion of the parent (256+) and the metabolite (272+). Separation was performed by a Luna C18 25 cm X 4.6 mm column using a generic gradient of 10% acetonitrile: 10mM Ammonium Acetate ascending to 100% in 20 minutes. Flow rate was 1.2 ml/min and injection volume was 25 µl.

RESULTS

Bioassays

Across a range of sap-feeding insect pests, sulfoxaflor exhibits activity that is on par with one of the leading sap-feeding insecticides, imidacloprid (Table 1). Sulfoxaflor was as active as imidacloprid against *M. persicae* and *L. hesperus* in laboratory bioassays, and significantly more active than imidacloprid against *A. gossypii*. Sulfoxaflor was less active than imidacloprid in bioassays against *B. tabaci*.

Compared to chloropyridyl sulfoximine analogue **2**, sulfoxaflor was significantly more active against the aphids *M. persicae* and *A. gossypii* (Table 1). Interestingly, there was no significant difference in activity between sulfoxaflor and **2** in assays involving *B. tabaci* or *L. hesperus* (Table 1).

Bioassays with several *B. tabaci* strains resistant to imidacloprid indicated that there was no appreciable cross-resistance to sulfoxaflor (Table 1). Likewise, a multi-resistant strain of *B. tabaci* that also has high levels of resistance to imidacloprid and other insecticides (*23*), showed no appreciable cross-resistance to both sulfoxaflor and **2**. Similarly, a multi-resistant strain of *M. persicae* (R – 4013A) that exhibits a high degree of resistance to deltamethrin and primicarb (*23*) and modest resistance to imidacloprid (17-fold), displayed no cross-resistance to either sulfoxaflor or sulfoximine **2** (Table 1).

UV Stability

In laboratory studies sulfoxaflor exhibited superior UV stability ($T_{1/2}$ = 88 hr) compared to imidacloprid ($T_{1/2}$ = 7hr) (Table 2). Likewise in efficacy studies under UV conditions, the control of *M. persicae* by sulfoxaflor was maintained at a high level over a period of seven days (Table 2). In contrast, the efficacy of imidacloprid, when applied

at the same rate under identical UV conditions, significantly declined over a seven day period (Table 2).

Metabolism Studies

Incubation of sulfoxaflor, imidacloprid or acetamiprid with D.mel-2 cells lacking the CYP6G1 gene resulted in complete recovery of each of the three compounds (Table 3). However, when incubated with D.mel-2 cells expressing the CYP6G1 gene, there was little recovery of either imidacloprid or acetamiprid (Table 3). In contrast there was complete recovery of sulfoxaflor in cells expressing CYP6G1 (Table 3), suggesting that sulfoxaflor is a poor substrate for the CYP6G1.

Mode of Action Studies

Initial observations on the effects of sulfoxaflor on *M. persicae* showed excitatory symptoms such as tremors, followed by paralysis and mortality, suggesting that the sulfoximines act via the insect nervous system. Similar symptoms were also noted for *D. melanogaster* and the American cockroach (*Periplaneta americana*) (G. Watson, personal observations). After preliminary mode of action analyses, sulfoxaflor was subsequently found to have an interaction with insect nAChRs. Like imidacloprid, sulfoxaflor was found to activate Dα2/β2 expressed in oocytes (e.g., Figure 6A). However, the maximal currents induced by sulfoxaflor were significantly larger than those induced by imidacloprid (Figure 6B). Additionally, sulfoxaflor displaced [^{3}H] imidacloprid in *M. persicae* tissue homogenates. However, the affinity of sulfoxaflor for

the [^{3}H] imidacloprid binding site was substantially weaker than that of imidacloprid (Figure 6C).

DISCUSSION

The sulfoximines, as exemplified by sulfoxaflor, represent a new class of insecticidal molecules that are chemically distinct. Sulfoxaflor is effective against a wide range of sap feeding insects including aphids, whiteflies, *Lygus* and plant hoppers (Table 1; *24*). Further, sulfoxaflor displays a high level of biological activity in the laboratory that is on par with, and in some instances superior to, the best current sap-feeding insecticides, the commercial neonicotinoids, such as imidacloprid (Table 1; *24*).

Compared to sulfoximine **2,** sulfoxaflor is substantially more active against the two aphid species examined (Table 1), but was similar in activity against the whitefly (*B. tabaci*) and *Lygus*. Thus, for these insect species, the replacement of the pyiridyl chlorine with CF_3 produced a marked improvement in aphid activity, while retaining the whitefly and *Lygus* activity of sulfoximine **2**. This observation is in contrast to the structure activity relationships for the nitromethylene analogs of imidacloprid on green rice leafhopper (*Nephotettix cincticeps*) where substitution of the pyridyl chlorine with a CF_3 resulted in a 25-fold decrease in activity (*25,26*).

In addition to the high level of insecticidal activity towards sap-feeding insect pests, available data for sulfoxaflor indicate a broad lack of cross-resistance in a variety of imidacloprid-resistant insect strains (Table 1; *23,24*). This same trend also appears to be true for species that exhibit resistance to multiple types of insecticides (i.e. organophosphates, carbamates, pyrethroids) (Table 1). For these multi-resistant strains

there was also no cross-resistance to sulfoxaflor, providing further support for the utility of sulfoxaflor against a broad range of insecticide resistant pest insect species. Further, this lack of cross-resistance also extends to sulfoximine **2**, providing additional evidence for the uniqueness of the sulfoximine insecticide class.

Sulfoxaflor displayed improved UV stability relative to imidacloprid. Further, in laboratory studies, sulfoxaflor was found to provide better *M. persicae* residual activity than imidacloprid. It is likely the much of the improvement in residual activity is due to the enhanced UV stability of sulfoxaflor.

Cytochrome P450 monooxygenases have been shown to play a role in imidacloprid resistance in several species including *N. lugens* (*27,28*), house fly (*Musca domestica*) (*29*), *M. persicae* (*30*), and *B. tabaci* (*31,32*). The lack of cross-resistance observed with sulfoxaflor suggests that it may not be susceptible to same monooxygenases that are responsible for degrading the neonicotinoids and other insecticides. A monooxygenase (CYP6G1) from *D. melanogaster* is responsible for resistance to range of insecticides including DDT and the neonicotinoids imidacloprid and nitenpyram (*33,34*). As a model system, the *CYP6G1* gene was cloned and expressed in the D.mel-2 cell line. Incubation of imidacloprid or acetamiprid with D.mel-2 cells expressing the *CYP6G1* gene, resulted in the complete metabolism (94-100%) of both neonicotinoids. In a total contrast, sulfoxaflor remained intact following incubation (Table 3), indicating that this particular monooxygenase (CYP6G1) is incapable of metabolizing sulfoxaflor. These data support the concept that the sulfoximines may not be susceptible to the same metabolic mechanisms (e.g., monooxygenases) responsible for resistance to the neonicotinoids and possibly other

insecticides. Thus, sulfoxaflor is a good fit for Insecticide Resistance Management (IRM) programs by not only providing a high level of efficacy against a wide variety of sap-feeding insect pests, but also by retaining efficacy against many insecticide-resistant sap-feeding insect strains.

Initial observations of the effects of sulfoxaflor on *M. persicae* were excitatory symptoms such as tremors, followed by paralysis and mortality, suggesting that the sulfoximines act on the insect nervous system. These same observations were also noted for *Drosophila* and the American cockroach (*Periplaneta americana*) (G. Watson, personal observations). Sulfoxaflor was subsequently found to be a nAChR agonist, as evidenced by its ability to activate Dα2/β2 receptors expressed in oocytes (Figure 6A,B). Dose-response studies showed that the maximal currents induced by sulfoxaflor were greater than those induced by imidacloprid (Figure 6B). The relatively low efficacy of imidacloprid has been observed in similar studies on both native (e.g., *35*) and expressed insect nAChRs (e.g., *36*). In addition, the affinity of sulfoxaflor for the [^{3}H]-imidacloprid binding site in *M. persicae* tissue was substantially weaker than that of imidacloprid. These results indicate that sulfoxaflor is a high efficacy nicotinic receptor agonist with relatively low affinity for the imidacloprid binding site. These observations further suggest that the interaction of sulfoxaflor with the insect nAChR is unique and distinguishable from that of imidacloprid. Further studies will be necessary to gain insight into the potentially complex interaction of sulfoxaflor with the nAChR.

Sulfoxaflor is the first insecticide in the new, unique class of insect control agents, the sulfoximines. Discovered by a scaffold-based approach and subsequent SAR-based structural modifications, sulfoxaflor exhibits broad spectrum, sap-feeding insect control

at levels that are comparable to the best commercial standards, including the neonicotinoids. Compared to the neonicotinoid imidacloprid, sulfoxaflor exhibits greater UV stability and as a consequence, improved residual insect control. Importantly, sulfoxaflor is highly effective against a variety of pest insect strains that are resistant to imidacloprid and a range of other insecticides. At least in part, the lack of cross-resistance appears to be associated with its novel chemistry in that sulfoxaflor is not susceptible to degradation by a cytochrome P450 monooxygenase such as CYP6G1 that is readily able to metabolize the neonicotinoids imidacloprid and acetamiprid. The novel sulfoximine chemistry of sulfoxaflor also translates to a unique set of interactions with nicotinic receptors that are distinct from those observed with the neonicotinoid, imidacloprid. Thus, sulfoxaflor possesses a combination of distinctive and favorable attributes that that suggest an excellent fit for many IRM programs.

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ABBREVIATIONS USED

SAR, structure activity relationships; IMI, imidacloprid; nAChR, nicotinic acetylcholine receptor; fi, fiducial limits; RR, resistance ratio;

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FIGURE CAPTIONS

Figure 1. Sulfoximine moiety – three sites for diversity

Figure 2. Temporal Development Leading to *N*-Nitro Sulfoximine Insecticide Lead. Using the sulfoximine structural scaffold (left), the aryloxyphenol sulfoximines (**A**) and the *N*-nitro substituted sulfoximines (**B**) ultimately led to the discovery of sulfoximine **1**, which had promising aphicidal activity.

Figure 3. Synthesis of targeted sulfoximines. Route A features the formation of a sulfoximine from a sulfoxide, whereas Route B utilizes a sulfilimine intermediate in route to targeted sulfoximines.

Figure 4. *N*-Cyano sulfoximine **2**

Figure 5. Sulfoxaflor

Figure 6. A. Sulfoxaflor induced current from Dα2/β2 receptors expressed in oocytes (sulfoxaflor applied to oocyte as indicated by horizontal line). B. Dose-dependence of sulfoxaflor (open bars) and imidacloprid (shaded bars) responses in Dα2/β2 receptors expressed in oocytes. C. Representative experiment showing relative displacement of [^{3}H] imidacloprid from *M. persicae* homogenates by sulfoxaflor (•) and imidacloprid (○).

TABLES

Table 1. Laboratory efficacies of sulfoxaflor and imidacloprid on sap-feeding insects.

Insecticide	Susceptible (strain) LC_{50} (95% fl)[1] ppm	Resistant (strain) LC_{50} (95% fl) ppm	RR[2]
	M. persicae (DAS Lab)	--	--
Sulfoxaflor	0.074 (0.049 – 0.101)		
Sulfoximine **2**	0.374 (0.199 – 0.484)		
Imidacloprid	0.090 (0.07 – 0.13)		
	M persicae (S – USIL)[3]	*M. persicae* (R – 4013A)[4]	
Sulfoxaflor	4.13 (2.25 – 6.82)	1.52 (0.644 – 2.65)	0.37
Sulfoximine **2**	62.3 (14.5 – 186.1)	12.5 (3.44 – 23.4)	0.20
Imidacloprid	0.896 (0.620 – 1.15)	15.3 (10.62 – 21.40)	17.1
	A. gossypii (DAS Lab)	--	--
Sulfoxaflor	0.20 (0.015 - 1.1)		
Sulfoximine **2**	3.0 (0.6 – 7.0)		
Imidacloprid	7.8 (2.4 - 15.6)		
	L. hesperus (DAS Lab)	--	--
Sulfoxaflor	2.78 (1.41 - 4.95)		
Sulfoximine **2**	1.69 (0.42 – 3.82)		
Imidacloprid	1.32 (0.48 - 2.61)		
	B. tabaci (DAS Lab)	--	--
Sulfoxaflor	0.85 (0.40 – 1.5)		
Sulfoximine **2**	0.29 (0.083 – 0.66)		
Imidacloprid	0.37 (0.18 – 0.63)		
	B. tabaci (DAS S)	*B. tabaci* (R - PBI)[5]	
Sulfoxaflor	2.8 (1.2 – 5.5)	6.4 (2.6 – 13.1)	2.3
Imidacloprid	0.20 (0.05 – 0.55)	174 (24.6 - >2000)	870
	B. tabaci (S - 4971BT1)[6]	*B. tabaci* (R – 4991BT1)[7]	
Sulfoxaflor	18 (13 - 24)	28 (25 - 55)	1.6
Imidacloprid	4.4 (2.8 – 6.1)	>1000 (--)	>230
	B. tabaci (S - 4971BT1)	*B. tabaci* (R – 4971BT9)[8]	
Sulfoxaflor	18 (13 - 24)	39 (25 - 55)	2.2
Imidacloprid	4.4 (2.8 – 6.1)	4500 (1900 - 29000)	1022

	B. tabaci (SUD – S)[9]	*B. tabaci* (R – CHLORAKA)[10]	
Sulfoxaflor	1.80 (0.84 – 3.13)	5.0 (3.13 – 7.76)	2.8
Sulfoximine **2**	4.48 (2.01 – 8.16)	13.2 (7.25 – 23.2)	2.9
Imidacloprid	1.23 (0.203 – 4.17)	>1000	>833

Some data adapted, in part, from Huang et al. (23) and Babcock et al. (24).

[1] fiducial limits
[2] resistance ratio – LC_{50} resistant strain / LC_{50} of susceptible strain
[3] Rothamsted susceptible laboratory strain
[4] Rothamsted strain collected from tobacco in Greece in 2000 -- resistant to pyrethroids, organophosphates, carbamates as well neonicotinoids - shows high levels (>50-fold) of resistance to deltamethrin
[5] DAS insecticide resistant B-biotype strain
[6] DAS susceptible reference strain
[7] Rothamsted resistant strain collected from Spain in 2008
[8] Rothamsted resistant Q-biotype strain collected from Spain in 2007
[9] Rothamsted susceptible laboratory strain
[10] Rothamsted Q-biotype strain collected from Cyprus in 2003 – shows resistance to pyrethroids, organophosphates and neonicotinoid insecticides.

Table 2. Effect of photolysis and UV light on the stabilities of sulfoxaflor and imidacloprid.

	Photolysis $T_{½}$ at 1000 ppm	UV chamber efficacy (% control) 0 DAA	3 DAA	7 DAA
Sulfoxaflor SC	88 hr	100	100	90
Imidacloprid SC	7 hr	100	42	21

Table 3. Metabolism of sulfoxaflor, imidacloprid and acetamiprid by D.mel-2 cells expressing *CYP6G1*.

	- CYP6G1[1] Mean % recovery (std)[3]	+ CYP6G1[2] Mean % recovery (std)
Sulfoxaflor	105.3 (4.4)	108.1 (2.5)
Imidacloprid	115.4 (8.6)	4.5 (0.9)
Acetamiprid	122.7 (29.4)	0.0 (0)

[1] cells lacking CYP6G1
[2] cells expressing CYP6G1
[3] % recovery 24 hrs after incubation compared to time 0: (standard deviation)

FIGURES

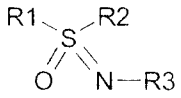


Figure 1.

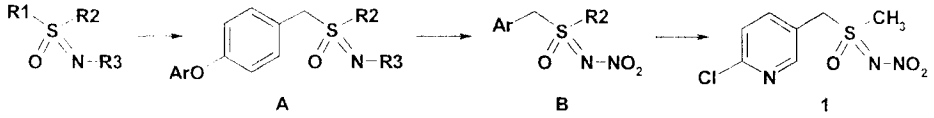
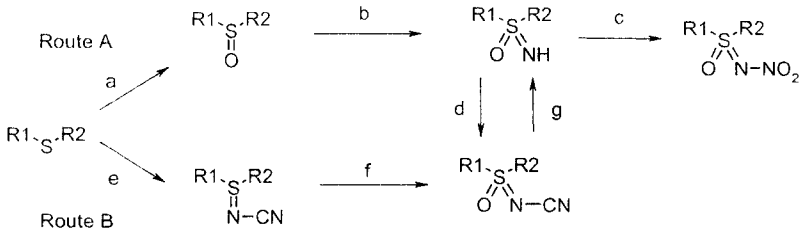


Figure 2.



a) *m*CPBA, CH_2Cl_2, -10 °C; b) NaN_3, H_2SO_4, $CHCl_3$; c) HNO_3, CH_2Cl_2; then Ac2O, reflux; d) BrCN, DMAP, CH_2Cl_2
e) H_2NCN, $PhI(OAc)_2$, THF, 0 °C; f) *m*CPBA, CH_2Cl_2, -10 °C; g) TFAA; then MeOH, K_2CO_3

Figure 3.

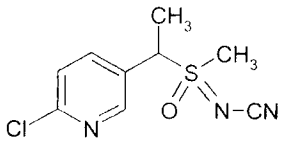


Figure 4.

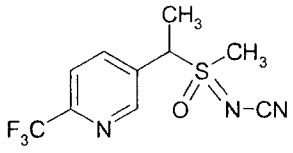


Figure 5.

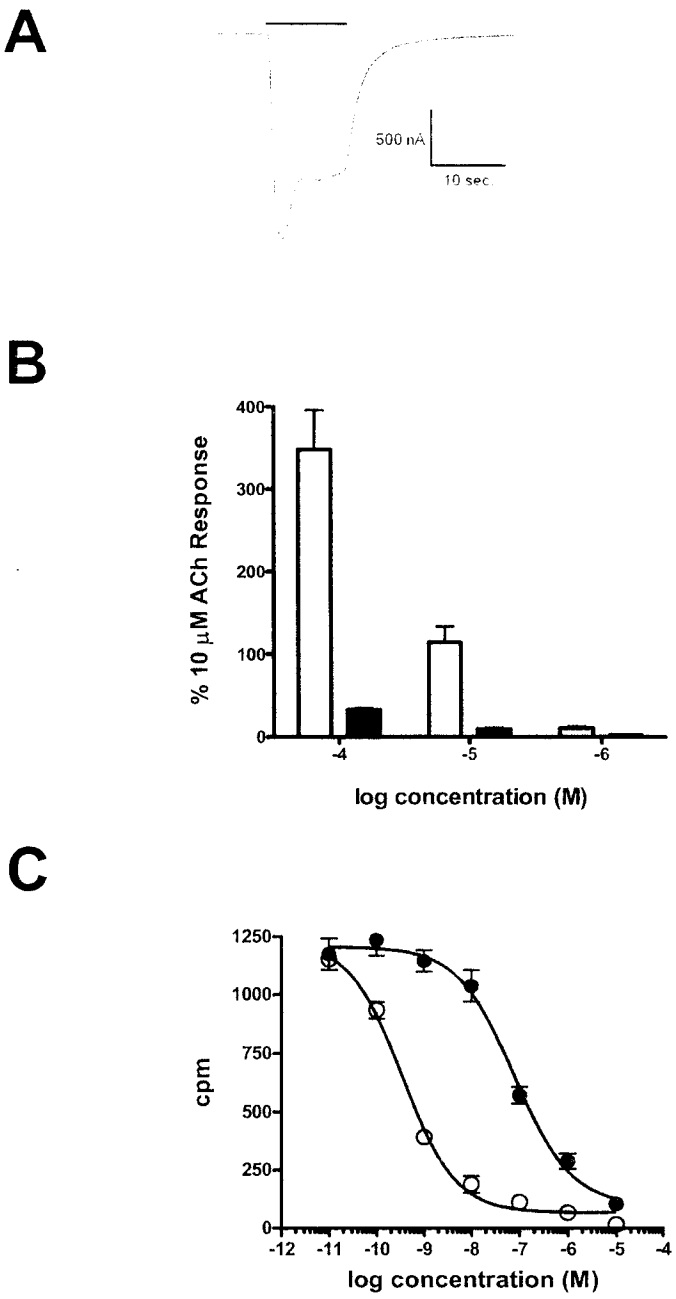

A
500 nA
10 sec
B
% 10 μM ACh Response
400
300
200
100
0
-4
-5
-6
log concentration (M)
C
cpm
1250
1000
750
500
250
0
-12
-11
-10
-9
-8
-7
-6
-5
-4
log concentration (M)

Figure 6.

Efficacy Arkansas

Project Title: Dow PB, 2009

GENERAL TRIAL INFORMATION

Study Director:	Gus Lorenz
Investigators:	Gus Lorenz, Kyle Colwell, Heather Wilf, Nichole Taillon
Location:	Marianna, Arkansas

CROP AND PEST DESCRIPTION

Pest:	Tarnished Plant Bugs
Crop:	Cotton
Planting Date:	May 18, 2009
Variety:	DPL 0924 BGIIRF
Plot Width, Unit:	12.5 ft.
Plot Length, Unit:	50 ft.
Replications:	4
Site Type:	field
Study Design:	Randomized Complete Block

APPLICATION DESCRIPTION

Application Dates:	4, 11 August 2009
Application Method:	Spray
Application Placement:	Foliar/ seed treatment

APPLICATION EQUIPMENT

Appl. Equipment:	Mud Master
Operating Pressure:	40 psi
Nozzle Type:	cone-jet
Nozzle Size:	Tee-Jet TXVS 6
Nozzle Spacing, Unit:	19in
Ground Speed, Unit:	3 mph
Carrier:	water
Spray Volume, Unit:	10
Propellant:	air pressure

MATERIALS AND METHODS

The trial was located in Marianna, Arkansas. Plot size was 12.5ft. X 50ft. Foliar insecticide applications were made with a mud master. Temik was applied in-furrow at planting at a rate of 5 lbs/a. Samples were taken on 7, 10, 14, 17, 26 August and 1 September, 2009. Insect numbers were determined by using a 2.5 ft. drop cloth. Two drop cloth samples were taken per plot for a total of 10 row ft per plot. Treatments followed by A were applied on 4 August, 2009. Treatments followed by AB were applied on 4 and 11 August 2009. Data was processed using Agriculture Research Manager Version 8. Analysis of variance was conducted and Duncan's New Multiple Range Test (P=0.10) to separate means.

RESULTS

Chart 1 Total Plant Bugs After 1st Application
Application Date**:** 4, August 2009
Rating Date: 7, 10 August 2009

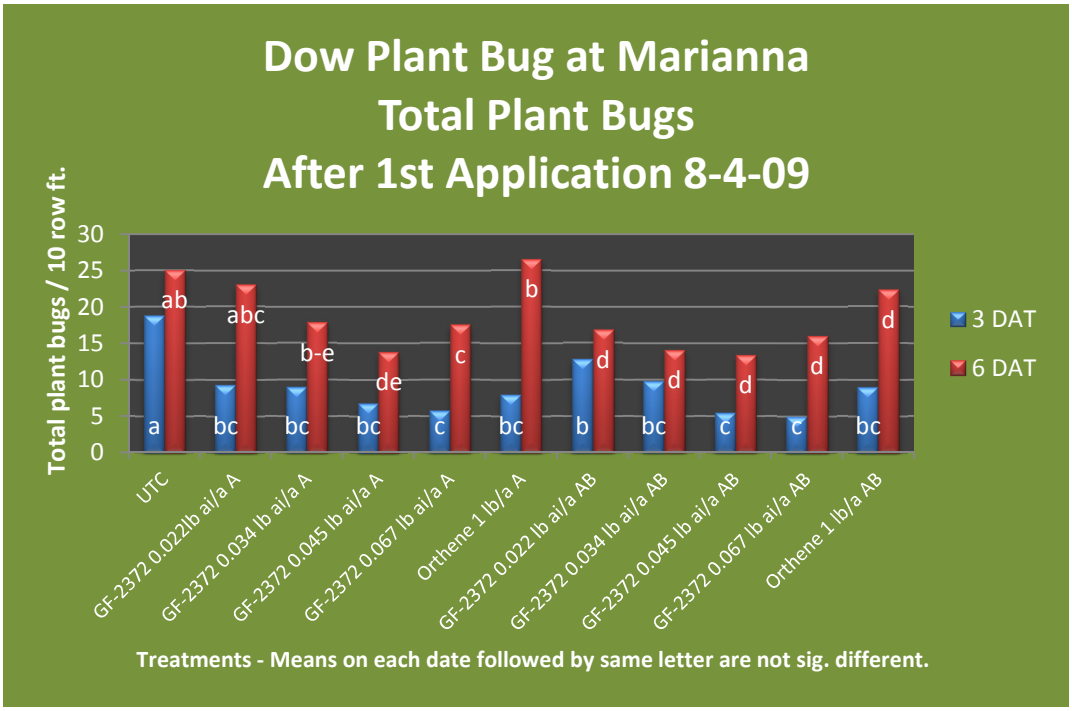


Table 1 Total Plant Bugs After 1st Application
Application Date**:** 4, August 2009
Rating Date: 7, 10 August 2009

Dow Plant Bug After 1st Application		
Treatments	**8/7/2009 3 DAT**	**8/10/2009 6 DAT**
UTC	18.8 a	25 ab
GF-2372 0.022lb ai/a A	9.3 bc	23 abc
GF-2372 0.034 lb ai/a A	9 bc	17.8 b-e
GF-2372 0.045 lb ai/a A	6.8 bc	13.8 de
GF-2372 0.067 lb ai/a A	5.8 c	17.5 b-e
Orthene 1 lb/a A	8 bc	26.5 a
GF-2372 0.022 lb ai/a AB	12.8 b	16.8 b-e
GF-2372 0.034 lb ai/a AB	9.8 bc	14 de
GF-2372 0.045 lb ai/a AB	5.5 c	13.3 e
GF-2372 0.067 lb ai/a AB	5 c	16 cde
Orthene 1 lb/a AB	9 bc	22.3 a-d

Chart 2 Total Plant Bugs After 2nd Application
Application Date**:** 11 August 2009
Rating Date: 14, 17, 26 August and 1 September, 2009

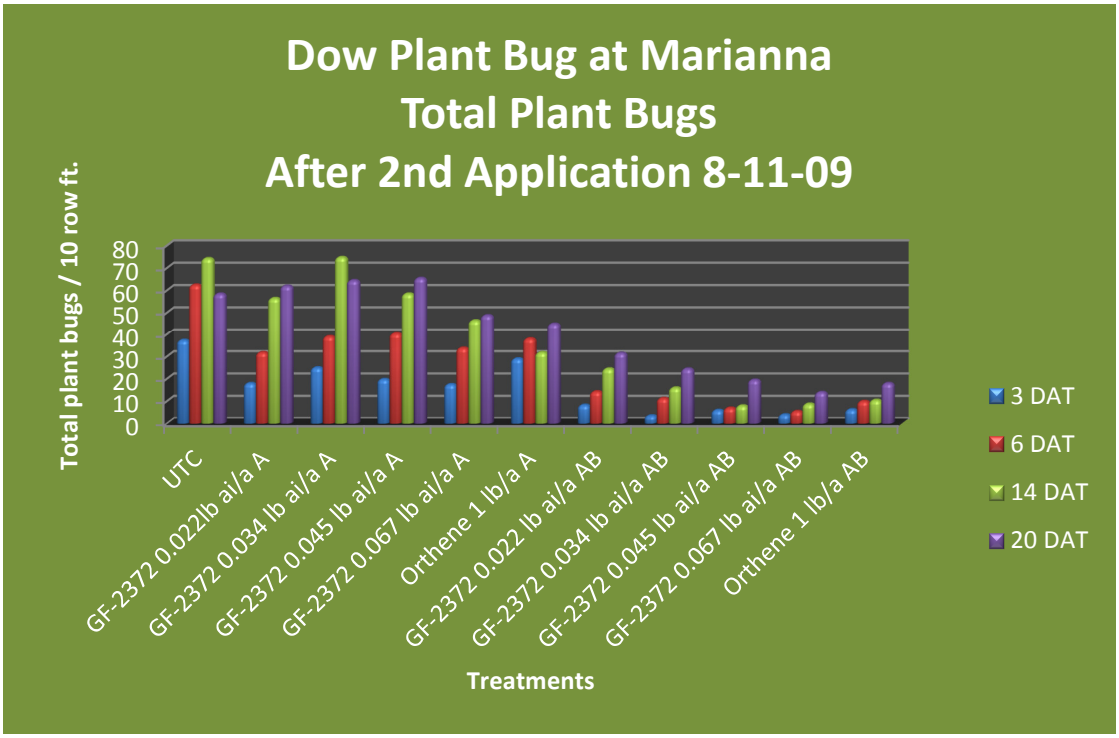


Table 2 Total Plant Bugs After 2nd Application
Application Date**:** 11 August 2009
Rating Date: 14, 17, 26 August and 1 September, 2009

Dow Plant Bug at Marianna After 2nd Application				
Treatments	**8/14/2009 3 DAT**	**8/17/2009 6 DAT**	**8/26/2009 14 DAT**	**9/1/2009 20 DAT**
UTC	37.3 a	62.5 a	74.3 a	58.5 ab
GF-2372 0.022lb ai/a A	18 c	31.8 b	56.5 b	62 ab
GF-2372 0.034 lb ai/a A	25 bc	39 b	74.8 a	64.5 a
GF-2372 0.045 lb ai/a A	19.8 c	40.3 b	58.5 b	65.5 a
GF-2372 0.067 lb ai/a A	17.5 c	33.8 b	46.5 b	48.8 abc
Orthene 1 lb/a A	29 b	38 b	31.8 c	45 bc
GF-2372 0.022 lb ai/a AB	8.3 d	14.3 c	24.5 cd	31.5 cd
GF-2372 0.034 lb ai/a AB	3.5 d	11.3 c	16 de	24.5 d
GF-2372 0.045 lb ai/a AB	6 d	7 c	8 e	19.5 d
GF-2372 0.067 lb ai/a AB	4 d	5.5 c	8.8 e	14 d
Orthene 1 lb/a AB	6.3 d	10 c	10.5 de	18 d

Chart 3 Seasonal Total Plant Bugs
Application Date**: 4,** 11 August 2009
Rating Date: 7, 10, 14, 17, 26 August and 1 September, 2009

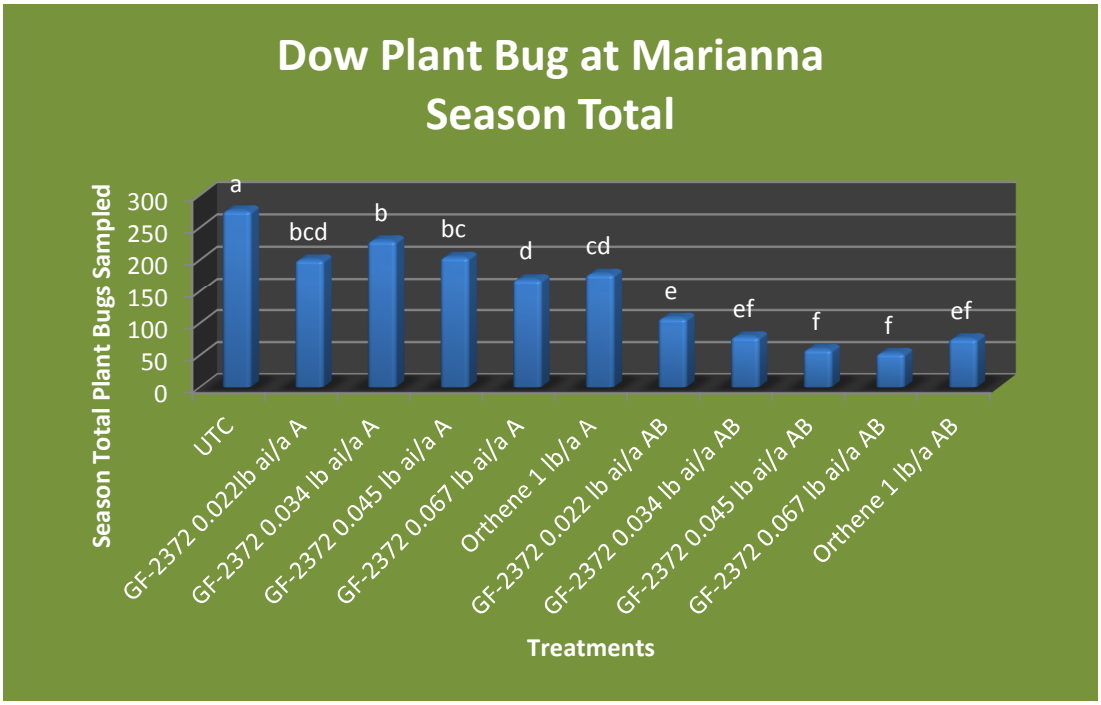


Table 3 Seasonal Total Plant Bugs
Application Date**: 4,** 11 August 2009
Rating Date: 7, 10, 14, 17, 26 August and 1 September, 2009

Dow Plant Bug Season Total		
Treatments	Total Plant Bugs	
UTC	276.3	a
GF-2372 0.022lb ai/a A	200.5	bcd
GF-2372 0.034 lb ai/a A	230	b
GF-2372 0.045 lb ai/a A	204.5	bc
GF-2372 0.067 lb ai/a A	169.8	d
Orthene 1 lb/a A	178.3	cd
GF-2372 0.022 lb ai/a AB	108	e
GF-2372 0.034 lb ai/a AB	79	ef
GF-2372 0.045 lb ai/a AB	59.3	f
GF-2372 0.067 lb ai/a AB	53.3	f
Orthene 1 lb/a AB	76	ef

Chart 4 Harvest Data
Planted: May 18, 2009
Harvested: November 12, 2009

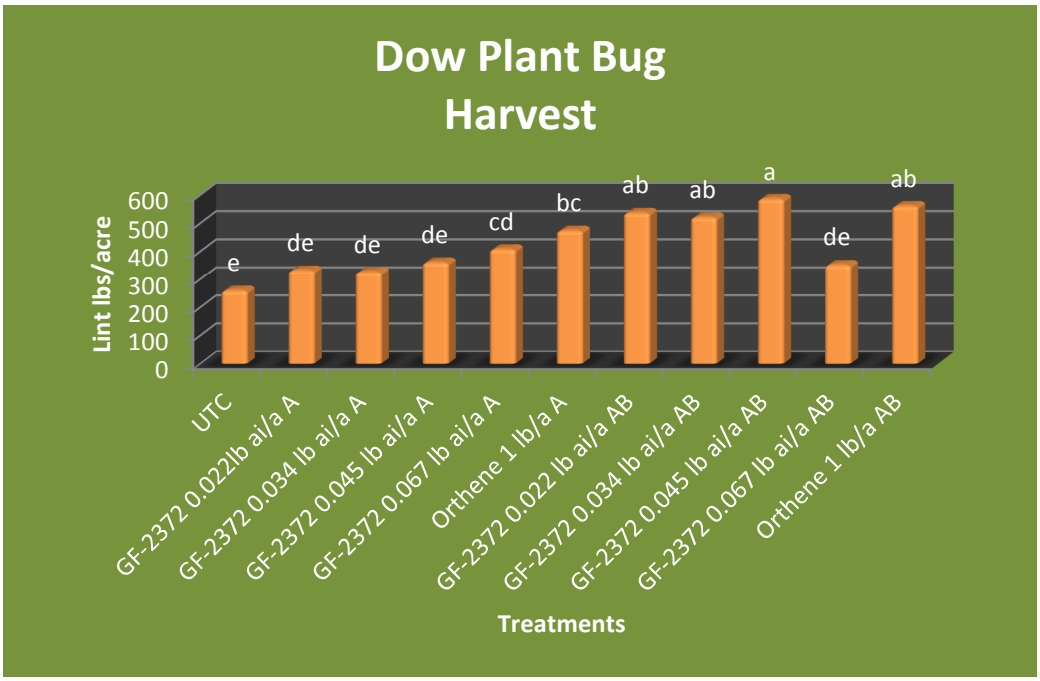


Table 4 Harvest Data
Planted: May 18, 2009
Harvested: November 12, 2009

Dow Plant Bug		
Treatments	Harvest Lint lbs/acre	
UTC	260.3	e
GF-2372 0.022lb ai/a A	332.8	de
GF-2372 0.034 lb ai/a A	327.3	de
GF-2372 0.045 lb ai/a A	362	de
GF-2372 0.067 lb ai/a A	409	cd
Orthene 1 lb/a A	474.8	bc
GF-2372 0.022 lb ai/a AB	537.8	ab
GF-2372 0.034 lb ai/a AB	521.8	ab
GF-2372 0.045 lb ai/a AB	587	a
GF-2372 0.067 lb ai/a AB	352.8	de
Orthene 1 lb/a AB	561.8	ab

 doi: 10.4182/amt.2010.F27

F27

COTTON: *Gossypium hirsutum*, 'Stoneville 4554 BG2RF'

EFFICACY OF FOLIAR INSECTICIDES AGAINST TARNISHED PLANT BUG ON COTTON (TEST 2), 2009

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Tarnished plant bug: *Lygus Lineolaris* (Palisot de Beauvois)'

Cotton was planted on a Marietta fine sandy loam soil in Washington Co., MS on 29 Jun. Plot size was 4 rows by 75 ft long planted on 38 inch centers. Statistical design was a RCB with 4 replications. Insecticides were applied with a tractor-mounted sprayer calibrated to deliver 10.0 gpa at 60 psi through TX-6 Hollow Cone nozzles (2 per row). The first application was made on 14 Aug. The 2nd and 3rd applications were made on 26 Aug and 9 Sep, respectively. Cotton was approximately at bloom stage at time of first application, but excessive plant bug injury had caused most fruit to abort. Control of immature tarnished plant bugs was determined by taking 2 (5row ft) drop cloth samples on 17 (3 DAT 1), 26 (12 DAT 1), and 31 (5 DAT 2) Aug., and 9 (14 DAT 2) and 14 (5 DAT 3) September. Data were analyzed with ANOVA and means were separated using a Fisher's Protected LSD ($P = 0.1$).

GF-2372 at the 0.067 lb AI/A rate effectively reduced immature tarnished plant bug densities below those in the untreated check and most other insecticide treatments on most sample dates. GF-2372 plus Brigade 2 EC was the most effective treatment. Orthene at 1.0 lb AI/A was also effective. Coragen 1.67 SC was least effective treatment.

Table 1.

Treatment/ Formulation	Rate lb (AI)/Acre	Average number of immature tarnished plant bugs per 5 row ft				
		3 DAT 1	12 DAT 1	5 DAT 2	14 DAT 2	5 DAT 3
GF-2372	0.045	3.5a	4.3b	2.3c	11.8cd	1.8de
GF-2372	0.067	1.8a	0.8d	0.0c	4.0d	0.8e
Orthene 90 S	1.0	2.5a	3.5bc	1.8c	4.8d	2.8cde
Brigade 2 EC	0.1	1.0a	1.5cd	1.0c	10.5cd	4.8c
Centric 40 WG	0.0625	3.0a	5.8ab	1.3c	17.5bc	4.3cd
Coragen 1.67 SC	0.088	3.0a	7.8a	7.8b	23.3ab	19.0b
GF-2372 + Brigade 2 EC	0.067 0.1	1.0a	1.5cd	1.0c	3.5d	0.5e
Untreated Check		2.5a	5.0b	12.3a	32.0a	24.9a
LSD (0.10)		2.81	2.65	3.71	9.05	2.62

Means within a column sharing the same letter are not significantly different (LSD; $P = 0.10$).

(F)
COTTON: *Gossypium hirsutum* (L.), 'DP 555 BG/RR'
EVALUATION OF SULFOXAFLOR (GF-2372) AGAINST TARNISHED PLANT BUGS IN COTTON, 2009

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Tarnished plant bug (TPB): *Lygus lineolaris* (Palisot de Beauvois)

Insecticide efficacy trials were conducted during 2009 at the Northeast Research Station (NERS) near St. Joseph, LA (Tensas Parish) and the Macon Ridge Research Station (MRRS) near Winnsboro, LA (Franklin Parish). Cotton seed was planted into a Commerce silt loam on 25 May at NERS (trial 1) and a Gigger silt loam on 1 Jun at MRRS (trials 2 and 3). Plot size was four to eight rows (40-inches on centers) X 50 ft with four replications. Insecticides were applied with a high-clearance sprayer and compressed air system calibrated to deliver 12 GPA through TeeJet TX-10 hollow cone nozzles (2/row) at 48 psi at NERS and at 9.5 GPA through TeeJet TX-8 hollow cone nozzles (2/row) at 50 psi at MRRS. In trial 1, insecticides were applied on 20 and 29 Jul, and post-treatment evaluations were made on 3 and 7 DAT1, 2, 7, and 12 DAT2. In trial 2, insecticides were applied on 3 Aug and post-treatment evaluations were made on 3, 8, 10, and 14 DAT. In trial 3, insecticides were applied on 25 Aug and post-treatment evaluations were made on 3, 7 and 10 DAT. Plots were sampled with a standard 2.5 x 2.5 ft black cloth shake sheet. In trials 1 and 2, two samples were taken on the center two rows (10 row ft total) of each plot. In trial 3, two samples were taken on rows 2 & 3 and rows 6 & 7 (20 row ft total) of each plot. Data were subjected to ANOVA and means separated according to DNMRT. Rainfall of 7.61, 1.46, and 0.4 inches occurred during trials 1, 2, and 3, respectively.

Across all test areas, pre-treatment numbers of TPB exceeded the action threshold of 2-3 insects/5 row ft established by the Louisiana Cooperative Extension Service. In trial 1, no insecticide treatment reduced TPB adults below that in the non-treated plots. At 3 and 7 DAT1, all insecticides except for sulfoxaflor (0.022 lb AI/acre) significantly reduced TPB nymphs below that in the non-treated plots. At 2DAT2, the 0.045 and 0.067 lb AI/acre rates of sulfoxaflor applied at timing A significantly reduced TPB nymphs compared to the non-treated control, while all insecticides applied twice (A and B) significantly reduced numbers of TPB nymphs below that in the non-treated control. At 7 DAT2, all plots treated once with insecticides had TPB nymphs similar to that in the non-treated control. All plots receiving the second application had fewer TPB nymphs compared to that in the non-treated plots at 7 and 12 DAT2. In trial 2, all insecticide-treated plots had significantly fewer TPB nymphs than that in the non-treated plots at 3 DAT. At 8 DAT, all insecticides significantly reduced TPB adults and nymphs compared to the non-treated control. Sulfoxaflor (0.034, 0.045, and 0.056 lb AI/acre) significantly reduced TPB adults and nymphs compared to the non-treated control at 10 DAT. In trial 3, sulfoxaflor (0.067 lb AI/acre) + Brigade, GF-2372 (0.045 lb AI/acre) + Brigade, Brigade, and Endigo significantly reduced TPB nymphs below that in the non-treated control at 3 DAT. By 7 DAT, only plots treated with sulfoxaflor (0.067 lb AI/acre) or sulfoxaflor (0.067 lb AI/acre) + Brigade had significantly lower numbers of TPB adults than the non-treated control plots. All sulfoxaflor treatments (alone and combined with Brigade) significantly reduced TPB nymphs compared to the non-treated, Brigade-treated, and Endigo-treated plots at 7 DAT. All insecticide-treated plots except Brigade had significantly fewer TPB nymphs compared to non-treated plots at 10 DAT. No phytotoxicity was observed with any treatment during these tests.

Trial 1.

Treatment/form.	Rate lb (AI)/acre	App.[a] Timing	No. TPB/5 row ft									
			3 DAT1		7 DAT1		2 DAT2		7 DAT2		12 DAT2	
			Adult	Nymph	Adult	Nymph	Adult	Nymph	Adult	Nymph	Adult	Nymph
Sulfoxaflor 50WG	0.022	A	0.3a	6.3abc	1.0a	9.3ab	1.5a	6.0abc	0.3b	11.5a	2.0a	10.5ab
Sulfoxaflor 50WG	0.034	A	1.3a	2.5cd	1.0a	6.0bc	0.3a	4.3abcd	0.5ab	11.0a	0.5b	7.5abc
Sulfoxaflor 50WG	0.045	A	0.3a	3.8bcd	0.8a	7.0bc	1.0a	3.8bcd	0.8ab	7.8abc	0.5b	7.5abc
Sulfoxaflor 50WG	0.067	A	0.3a	2.0cd	0.3a	6.0bc	1.3a	3.8bcd	0.5ab	8.8ab	0.3b	6.5bcd
Orthene 90SP	1.0	A	0.8a	2.0cd	1.5a	5.5bc	0.3a	8.0ab	0.5ab	7.5abc	0.5b	8.5ab
Sulfoxaflor 50WG	0.022	A+B	0.5a	9.0a	1.8a	7.8bc	0.8a	3.0cd	0.0b	3.3cd	0.0b	4.3cde
Sulfoxaflor 50WG	0.034	A+B	1.3a	6.5abc	1.5a	5.3bc	1.0a	2.3cd	1.8a	4.3bcd	0.0b	3.8cde
Sulfoxaflor 50WG	0.045	A+B	0.0a	2.0cd	1.0a	6.8bc	0.5a	1.8cd	0.5ab	5.3bcd	0.5b	2.5de
Sulfoxaflor 50WG	0.067	A+B	0.0a	1.0d	0.8a	3.8c	0.3a	0.3d	0.8ab	2.3d	0.3b	3.5cde
Orthene 90SP	1.0	A+B	0.0a	2.0cd	1.3a	5.5bc	0.3a	1.3d	0.5ab	2.0d	0.0b	1.3e
Non-treated	----		1.0a	7.0ab	1.8a	13.0a	1.5a	8.3a	0.3b	11.8a	1.0ab	10.8a
P>F (ANOVA)			0.12	<0.01	0.83	0.01	0.19	<0.01	0.32	<0.01	0.04	<0.01

Means within columns followed by the same letter are not significantly different (DNMRT, P = 0.05).
[a] Application timing: A application on 20 Jul; B application on 29 July.

Trial 2.

Treatment/form.	Rate lb (AI)/acre	No. TPB/5 row ft							
		3 DAT		8 DAT		10 DAT		14 DAT	
		Adult	Nymph	Adult	Nymph	Adult	Nymph	Adult	Nymph
Sulfoxaflor 50WG	0.022	3.4a	6.6b	1.6b	5.6b	1.0b	4.8a	0.4a	2.2a
Sulfoxaflor 50WG	0.034	1.0a	4.6b	0.6b	3.2bc	0.6b	2.6b	0.6a	1.8a
Sulfoxaflor 50WG	0.045	1.8a	3.4b	1.0b	2.4c	0.8b	1.6b	0.4a	1.0a
Sulfoxaflor 50WG	0.056	1.2a	4.4b	0.6b	2.2c	0.6b	1.2b	0.4a	0.8a
Sulfoxaflor 50WG	0.067	2.2a	4.4b	0.8b	1.8c	1.8ab	1.2b	0.4a	0.6a
Orthene 90SP	1.0	1.6a	4.6b	1.0b	3.6bc	1.2ab	2.2b	0.4a	0.8a
Centric 40WG	0.047	2.4a	6.6b	0.6b	1.6c	2.0ab	1.8b	0.4a	0.8a
Non-treated	----	2.8a	12.0a	3.4a	10.4a	2.6a	4.6a	0.8a	2.6a
P>F (ANOVA)		0.23	<0.01	<0.01	<0.01	0.03	<0.01	0.98	0.08

Means within columns followed by the same letter are not significantly different (DNMRT, P = 0.05).

Trial 3.

Treatment/form.	Rate lb (AI)/acre	No. TPB/5 row ft					
		3 DAT		7 DAT		10 DAT	
		Adult	Nymph	Adult	Nymph	Adult	Nymph
Sulfoxaflor 50WG	0.067	3.0a	11.3abc	0.0c	0.8c	2.8a	4.8b
Sulfoxaflor 50WG	0.067	1.8a	9.8bc	0.3bc	2.5c	1.5a	3.5b
+ Brigade 2EC	0.03						
Sulfoxaflor 50WG	0.045	2.3a	14.0abc	1.8ab	3.8c	1.3a	5.5b
Sulfoxaflor 50WG	0.045	1.5a	7.3c	1.5abc	3.0c	2.3a	5.5b
+ Brigade 2EC	0.03						
Sulfoxaflor 50WG	0.022	3.3a	16.3ab	1.0bc	3.8c	0.5a	6.0b
Sulfoxaflor 50WG	0.022	3.0a	10.5abc	1.5abc	4.3c	3.3a	6.0b
+ Brigade 2EC	0.03						
Brigade 2EC	0.03	1.5a	9.8bc	2.8a	15.8a	2.8a	17.0a
Endigo 2.06SC	0.0885	2.5a	9.0c	1.3abc	10.3b	1.8a	8.3b
Non-treated	----	1.8a	17.5a	1.8ab	14.0ab	1.0a	16.8a
P>F (ANOVA)		0.66	0.04	0.04	<0.01	0.09	<0.01

Means within columns followed by the same letter are not significantly different (DNMRT, P = 0.05).

(F)
COTTON: *Gossypium hirsutum* (L.), 'DP 555 BG/RR'
EVALUATION OF SULFOXAFLOR (GF-2372) AND STANDARD INSECTICIDES AGAINST TARNISHED PLANT BUGS IN COTTON, 2010

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Tarnished plant bug (TPB): *Lygus lineolaris* (Palisot de Beauvois)

An insecticide efficacy trial was conducted during 2010 at the Northeast Research Station (NERS) near St. Joseph, LA (Tensas Parish). Cotton seed was planted into a Commerce silt loam on 12 May. Plot size was four rows (40-inch centers) X 55 ft with four replications. Insecticides were applied with a high-clearance sprayer and compressed air system calibrated to deliver 12 GPA through TeeJet TX-10 hollow cone nozzles (2/row) at 48 psi. Insecticides were applied on 1 and 9 Jul, and post-treatment evaluations were made on 4 and 8 DAT1, and 3 and 7 DAT2. Plots were sampled with a standard 2.5 x 2.5 ft black cloth shake sheet. Two samples were taken on the center two rows (10 row ft total) of each plot. Data were subjected to ANOVA and means separated according to DNMRT. Rainfall of 1.53 inches occurred during the test period.

Across the test area, pre-treatment numbers of TPB exceeded the action threshold of 2-3 insects/5 row ft established by the Louisiana Cooperative Extension Service. All insecticide-treated plots significantly reduced TPB below that in the non-treated control plots at all sample intervals except 3 DAT2. All insecticides significantly lowered seasonal total TPB below that in the non-treated control. In addition sulfoxaflor (0.067 lb AI/acre) and Diamond + sulfoxaflor reduced the seasonal total TPB compared to sulfoxaflor (0.045 lb AI/acre) and Orthene. No phytotoxicity was observed with any treatment during these tests.

Treatment/form.	Rate lb (AI)/acre	No. TPB/5 row ft [a] 4 DAT1	8 DAT1	3 DAT2	7 DAT2	SEASON TOTAL
Sulfoxaflor 50WG	0.045	4.0b	2.8bc	1.8a	0.5b	9.0b
Sulfoxaflor 50WG	0.067	2.3b	1.8bc	0.8a	0.3b	5.0c
Orthene 90SP	1.0	2.8b	4.0b	1.5a	1.0b	9.3b
Endigo 2.06SC	0.088	3.0b	3.3bc	0.5a	0.5b	7.3bc
Bidrin 8EC	0.5	1.8b	1.8bc	2.0a	1.0b	6.5bc
Diamond 0.83EC	0.039	2.3b	1.5c	0.8a	0.8b	5.3c
+ Sulfoxaflor 50WG	+0.045					
Diamond 0.83EC	0.039	3.3b	2.3bc	1.8a	1.0b	8.3bc
Non-treated	----	8.8a	6.8a	1.5a	2.8a	19.8a
P>F (ANOVA)		<0.01	<0.01	0.79	0.04	<0.01

Means within columns followed by the same letter are not significantly different (DNMRT, P = 0.05).
[a] Cumulative TPB adults and nymphs.

Appendix: Efficacy Data

A) Summary of multi-state (AR, LA, MS, TN) efficacy trials of sulfoxaflor against "high pressure" tarnished plant bug populations on cotton in 2008-2010 seasons.

Data from a total of 27 "high pressure" tarnished plant bug (TPB) efficacy trials are reported in this summary. High pressure trials were defined as those where the plant bug population in untreated plots averaged at least 3-fold higher than the economic threshold (3 plant bugs/5 row feet) over the course of the trial. These trials demonstrate efficacy under extreme pest pressure. On average, TPB populations were four to five-fold the economic threshold in untreated plots.

Included in this summary are trials conducted by universities as well as internal Dow AgroSciences trials. All insecticide applications were made by ground. Plant bug numbers were assessed at various days after application using a drop cloth placed between rows. Sections of row were shaken over the cloth and plant bugs falling on the cloth were counted. Data reported here are for plant bug nymphs only, because nymphs are less mobile and a more reliable indicator of efficacy in small plots.

Results: Under extreme pest pressure (TPB populations averaging >5-fold economic threshold), no product reduced average populations below threshold with a single application (Table 1). After a second application, most products except for dicrotophos at 2-5 days after application two and thiamethoxam at 6-8 days after application two reduced the average number of TPB below the economic threshold. However, by 9-12 days after the second application, only sulfoxaflor at both rates and acephate reduced the average number of TPB below threshold, with sulfoxaflor providing the greatest reduction on average. These data demonstrate extended residual control provided by sulfoxaflor and the need for multiple insecticide applications to maintain TPB populations below threshold under high pest pressure.

Table 1. Summary of tarnished plant bug control in 27 "high pressure" trials.

Insecticide	Rate (oz ai/acre)	# Plant Bug Nymphs at Each Evaluation Interval (days after application one (DAA1) and two (DAA2)			
		2-5 DAA1	2-5 DAA2	6-8 DAA2	9-12 DAA2
Sulfoxaflor	0.71	4.9	2.3	1.5	2.7
Sulfoxaflor	1.07	4.2	1.5	1.1	2.4
Acephate	16.0	3.3	1.6	1.8	2.8
Dicrotophos	8.0	7.1	4.0	1.0	10.1
Thiamethoxam	0.80	4.7	2.3	3.6	8.0
Thiamethoxam + L-cyhalothrin	0.66 + 0.50	6.1	1.8	1.6	4.4
Untreated		15.8	15.0	12.4	12.4

B) Yield response to sulfoxaflor and acephate applied for plant bug control.

A subset of 16 high pressure trials during this time period were carried to yield and compared to acephate, the most effective commercial standard. It should be noted that the yield response demonstrated here is based only on two applications of insecticide being skipped in "untreated" plots. During the course of the season, "untreated" plots were treated at other times to control plant bugs and keep the plots in a manageable condition such that they could be harvested. Much greater reductions in yield would be expected if plots were untreated through the entire course of the season.

Applications of sulfoxaflor produced very similar yields, on average, as that of the most effective commercial standard.

Table 2. Cotton yield response to two treatments of sulfoxaflor or acephate.

Treatment	Rate (oz ai/acre	Yield (lbs lint/acre)
Sulfoxaflor	0.71	988
Sulfoxaflor	1.07	965
Acephate	16.0	972
Untreated		664

C) Performance of sulfoxaflor as part of a season-long control program for plant bugs.

In 2010 trials were initiated to compare sulfoxaflor as part of a season long program. Plant bug management in grower fields requires multiple applications and products are typically rotated to minimize the selection pressure on individual products. This trial was conducted by Dow AgroSciences at Wayside, MS and compared programs that included rotation of sulfoxaflor and acephate to a program that included a rotation of the most commonly used commercial standards (Table 3).

Table 3. Programs evaluated for season-long plant bug control. Rates of each treatment are given in oz ai/acre.

	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5
Program 1	Sulfoxaflor 0.71	Sulfoxaflor 0.71	Acephate 16.0	Sulfoxaflor 0.71	Sulfoxaflor 0.71
Program 2	Sulfoxaflor 1.07	Sulfoxaflor 1.07	Acephate 16.0	Sulfoxaflor 1.07	Sulfoxaflor 1.07
Program 3	Acephate 8.0 + Novaluron 0.62	Dicrotophos 8.0	Thiamethoxam 0.77 + Lambda-cyhalothrin 0.57	Acephate 12.0 + Lambda-cyhalothrin 0.64	Acephate 16.0

Results: Programs that incorporated sulfoxaflor at proposed use rates maintained plant bug populations below the economic threshold for the duration of the trial (Table 4). A program consisting of commercial standards failed to reduce populations below the economic threshold at several evaluations, and populations were significantly reduced in

sulfoxaflor-treated plots compared to the commercial program at some evaluations. Yield in the programs that included sulfoxaflor was significantly greater than that of the commercial standard program, and the commercial standard program had significantly greater yield than the untreated (Table 5).

Table 4. Efficacy of three programs for season-long plant bug control.

	Number of Plant Bug Nymphs/5 Row Feet[1]				
	3 DAA1	7 DAA2	6 DAA3	4 DAA 4	3 DAA 5
Program 1	0.88 b	0.38 c	2.8 bc	2.0 b	1.3 b
Program 2	1.50 b	0.50 c	2.3 c	1.0 b	1.3 b
Program 3	1.38 b	5.88 b	9.0 ab	3.5 b	1.0 b
Untreated	7.88 a	9.50 a	9.5 a	10.0 a	4.5 a

[1]Means followed by the same letter are not significantly different (P = 0.1, Tukey's HSD).

Table 5. Yield response to three programs for season-long plant bug control.

	Cotton Yield (lbs lint/acre)[1]
Program 1	1266 a
Program 2	1266 a
Program 3	1019 b
Untreated	604 c

[1]Means followed by the same letter are not significantly different (P = 0.1, Tukey's HSD).

PERFORMANCE OF DOW AGROSCIENCES' SULFOXAFLOR INSECTICIDE AGAINST TARNISHED PLANT BUG, *LYGUS LINEOLARIS*, IN MID-SOUTH COTTON

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Abstract

Sulfoxaflor is a new proprietary insecticide within a novel chemical class developed by Dow AgroSciences. Sulfoxaflor insecticide is active against a broad range of sap-feeding insects including aphids, *Aphis gosypii*, Tarnished plant bugs, *Lygus lineolaris,* whiteflies, planthoppers, and scales. Research has demonstrated sulfoxaflor to be active against target pests at low rates, to provide fast knockdown, and extended residual control. Sulfoxaflor was characterized for activity against tarnished plant bug, *Lygus lineolaris*, in the mid-south U.S. cotton during 2008-2009. A robust testing program included 32 trials in 10 locations, conducted by both public and private researchers. Sulfoxaflor insecticide was evaluated over a wide range of environmental conditions and tarnished plant bug infestation levels.

Results from two years of testing demonstrated sulfoxaflor insecticide (0.045 lb ai/acre) provided knockdown of tarnished plant bug infestations at ≤ 5 d and residual control for ≥ 7 d. In addition, cotton treated with sulfoxaflor protected lint yield equal to or superior than cotton treated with acephate (1.0 lb ai/acre) in 16 trials. As with most insecticides, the performance of sulfoxaflor in cotton will be dependent upon tarnished plant bug population level and intensity of infestation. Based upon the two years of research, multiple applications of sulfoxaflor may be required and the interval between applications may vary in cotton for tarnished plant bug management. Sulfoxaflor insecticide will have an excellent fit in cotton IPM programs based on the molecule's spectrum and properties, as a rotational partner with other chemistries, and as a tool for management of insect resistant populations. Recommended scouting techniques for tarnished plant bugs and IPM practices should continue to be utilized. Registration of sulfoxaflor for U.S cotton is anticipated in 2012.